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Economic evaluation of five strategies for the prevention of neonatal group B streptococcal (GBS) disease in Alberta

by

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The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies for acceptance, a thesis entitled "Economic evaluation of five strategies for the prevention of neonatal group B streptococcal (GBS) disease in Alberta." submitted by Sakina Raj in partial fulfillment of the requirements for the Master of Science, Epidemiology.

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Abstract

There is substantial morbidity and mortality associated with group B streptococcal (GBS) disease among Canadian neonates. While the adoption of standard preventive strategies to minimize the risk of GBS disease in Canada may have considerable economic impact not only on the well being of pregnant women and newborns, but also on resource use, the impact has never been quantified. The objective of this study was to compare the costs and effectiveness of five strategies for the prevention of neonatal GBS disease in Alberta.

This study used an economic evaluation-decision analysis, evaluating five strategies namely 1) no intervention 2) risk factor based 3) screening at 35-37 weeks 4) screening at 26-28 weeks and 5) vaccination, using the perspective of the health care payer (Calgary Health Region and other health care sectors). Data on costs were collected from the Calgary Health Region Corporate Data, and other input data and probabilities were taken from active-surveillance studies of GBS in Alberta and the current literature. Sensitivity analysis was performed to check the robustness of the results and aid the decision-making process in different settings.

In the baseline analysis, at a incidence rate of 1.2 per 1000 live births in Alberta (46 cases per 38,000 average deliveries), average costs per case prevented were $8 thousands, $26 thousands and $31 thousands for strategy 2, strategy 5, and strategy 3, respectively. The ratio of the incremental cost and the incremental effectiveness, an incremental cost effectiveness ratio (ICER) of $75,000 was generated between strategy 2 and 5 and an ICER of $92,000 between strategy 5 and 3. Strategy 3 was considered the most effective as it prevents 86 % of GBS cases, but it is costly compared to strategies 2

and 5. Strategy 4 was dominated by strategy 5 (vaccination) and thus eliminated from consideration. Strategy 2 was the least expensive but it prevents only 59% of cases compared to 79% using strategy 5 (vaccine is not yet available). Sensitivity analysis showed that variation in estimates did not have an impact on cost-effectiveness ranking of the prevention strategies. The analysis indicated that strategy 3 is the most effective but is costly, strategy 2 is the least expensive but is less effective than strategy 3 and 5. Whether strategy 3 is considered cost-effective depends on whether an incremental cost per case prevented of $92,000 is considered acceptable.

This cost effectiveness analysis (CEA) for GBS prevention has implications for future research and policy. It supports the SOGC and CDC recommendations that GBS prevention strategy in some form is warranted. It also indicates that strategy 3 (screening at 35-37 weeks) is the most effective strategy. While some guidelines are provided in this thesis, it should be noted that careful interpretation of the results is required for decision-making.

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Dedication

This thesis is dedicated to my husband Mustansir H. Raj, my children Mustaali, Nurunnisa and Aziz Ahmad Raj and my parents Shamoon Ali and Amina Habib, for their love and support in all my endeavors.

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CHAPTER ONE: INTRODUCTION

1.1 Introduction

There is substantial morbidity and mortality associated with invasive *Streptococcus agalactiae* or group B streptococcal (GBS) disease among Canadian neonates [1]. GBS can cause life-threatening infections, sepsis, pneumonia, and meningitis in newborns. Infants acquire this infection perinatally, primarily through birth canal exposure of colonized mothers [2]. Intrapartum antimicrobial prophylaxis (IAP) can prevent most neonatal GBS infections (an estimated 41% using a risk-based strategy and 78% using a screening based strategy) in women whose infants are at increased risk for infection [3]. However, despite clinical trials that demonstrate the effectiveness of IAP, debate about the most effective strategy for identifying candidates for IAP continues. A GBS vaccine that elicits high concentrations of transplacentally transmissible immunoglobin-G (IgG) may also prevent this devastating infection [4]. GBS polysaccharide-protein conjugate vaccines are being evaluated in clinical trials. Presently, however, evaluation of their potential cost-effectiveness is important for determining future practice options.

Although the incidence of neonatal GBS disease is declining, preventable cases continue to occur [5, 6]. These declines are likely a result of modest implementation of both risk- and screening-based expert guidelines and improved laboratory detection practices [7]. There has been considerable economic burden associated with cases of neonatal GBS in the US, but there are currently no analyses of the resource burden incurred as a result of this disease in Canada, nor of comparative costs of various potential prevention strategies (Table 1).

Study Relevance

The adoption of standard and universal screening policies, IAP, and other preventive strategies to minimize the risk of GBS disease in Canada may have considerable economic impact, not only on the well being of pregnant women and their newborns but also on resource use, yet the impact has never been quantified. This is

because most infections are acquired in-utero, and all of the current prevention strategies are directed towards pregnant women during labor to reduce transmission of GBS disease from mothers to infants. Clinicians and health care managers, in both obstetrics and pediatrics, are currently faced with the dilemma of choosing the best strategy for reducing GBS early-onset disease in terms of health outcomes, medical costs, how best to identify which women should receive IAP, and consistency in implementation of these strategies. In Canada, information on the cost-effectiveness of any preventive strategy is lacking.

In this study, some of the issues outlined above are addressed by using decision analysis models and economic analysis to compare the cost-effectiveness of five strategies (Table 1) using 1992 rates of GBS early-onset disease [1] to predict the impact of these prevention strategies on neonatal disease and medical costs in Alberta.

Table 1: Five group B streptococcal disease prevention strategies evaluated in this study.

Strategies	
1	No intervention
2	No screening, IAP to women with risk factors.
3	Screening at 35-37 weeks and IAP to all colonized women
4	Screening at 26-28 weeks and IAP to colonized women with risk factors
5	GBS vaccination

For more details see prevention strategies section 2.1
IAP: Intra-partum antibiotic prophylaxis
GBS: Group B streptococcus

Organization of the thesis

After the introduction and study relevance in Chapter One, the objectives of the study are outlined. Chapter Two provides background information and a literature review of group B streptococcal infections (GBS), including various prevention strategies and limitations of current knowledge. The basic concepts of economic evaluation, the differences between various economic evaluations, the concepts of decision analysis, the framework used to set up the decision analytic model, as well as

an explanation of sensitivity analysis are also included in Chapter Two. Chapter Three describes the methodology used to obtain the data on costs, health outcomes, probabilities, decision tree construction, and assumptions. In Chapter Four, the results of baseline analysis and sensitivity analysis are presented, respectively. Chapter Five includes the discussion, strengths and limitations of the study. Chapter Six concludes with a summary on the important findings of this study, their implications, and some future research options.

1.2 Objectives of the study

Primary Objective

- To compare the costs and effectiveness of five strategies (Table 1) for the prevention of neonatal GBS disease in Alberta.

Secondary Objectives

- To estimate the cost of a case of group B streptococcal early-onset disease (GBS-EOD) and the costs of the five prevention strategies in Alberta.
- To determine the probability of occurrence of important clinical events in the decision pathway for each strategy and the costs associated with each event.
- To estimate the magnitudes of outcomes (e.g., number of cases prevented) associated with each event.
- To find the preferred strategy for reduction of GBS-EOD and its sequelae.

CHAPTER TWO: BACKGROUND

2.1 Group B streptococcal literature review

Group B streptococcus (*Streptococcus agalactiae*) is a gram-positive coccus (bacterium) that commonly colonizes pregnant women's vaginas. Colonized women have the potential of transmitting GBS to their infants vertically (Figure 1) or in rare cases, by hematogenous spread (i.e., disseminated by the blood circulation). The colonized women may be asymptomatic, so cultures are required to diagnose the presence of GBS in the vaginal or rectal areas. The key step in preventing neonatal disease is detecting intrapartum maternal genital tract colonization in order to identify a mother at risk [8].

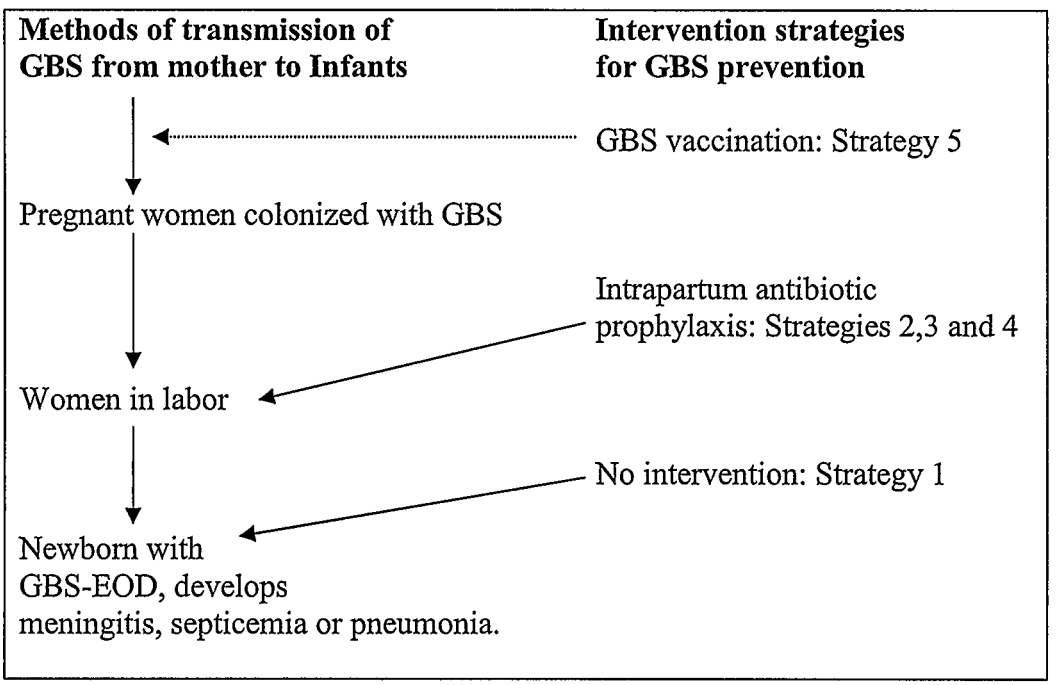


Figure 1: Methods of group B streptococcus transmission.

GBS-EOD: Group B streptococcal-early onset disease.

Two forms of GBS disease in infants are well recognized (Table 2). Early-onset disease (EOD) is defined as isolation of GBS from a normally sterile site (e.g., blood, and/or cerebrospinal fluid) in an infant less than seven days of age with clinical

symptoms and signs compatible with a systemic infection. Prior to implementation of current guidelines, EOD accounted for 80% to 85% of neonatal infections. EOD has a higher mortality rate and is acquired through vertical transmission from colonized mothers. Exposure of the neonate to the organism occurs either by an ascending route in utero through ruptured or intact membranes, or by acquisition during passage through the birth canal. The three most common clinical presentations include sepsis, pneumonia, and meningitis. Late-onset disease (LOD) usually occurs in infants between one week and up to three months of age, with meningitis being the most common clinical presentation (85% of cases) [9]. LOD is acquired either by vertical transmission (delayed infection after early colonization in 50% of the cases) [10] or by horizontal transmission (due to cross infection in the hospital from healthcare workers or in the community) [11]. The potential effect of IAP on LOD is not known [19], and so the present study assumes that IAP has no specific effect on LOD, but an effective vaccine would likely prevent both EOD and LOD [18]. GBS also causes chorioamnionitis, urinary tract infection, and puerperal wound infection [12, 13] in pregnant women. Despite the apparent effectiveness of IAP in preventing EOD, uncertainty remains regarding the best preventive strategy.

Table 2: Description of group B streptococcal disease (GBS) in newborns according to the age of onset.

Onset	Definition and signs at presentation	Incidence	% Mortality
Early (EOD)	-Occurs in infants <1 week old -Acquired through vertical transmission from colonized mothers -Clinical presentations include sepsis, pneumonia and meningitis[6]	0.42 per 1000 total births in Alberta during 1995-1999 [6]	9.0 [6]
Late (LOD)	-Occurs in infants one week or older -Acquired either by vertical transmission (delayed infection after colonization in 50% of cases) or by horizontal transmission (in hospital or in the community -Meningitis is the most common presentation (in 33 % of cases) [1]	0.22 per 1000 total births in Alberta during 1995-1999 [6]	2.0 [6]

EOD: Early-onset disease LOD: Late-onset disease

Epidemiology

Group B streptococcus has historically been the most important cause of bacterial sepsis and meningitis among newborns [2], although incidence rates of proven infection have declined recently [5, 7]. In 1990, there were over 15,000 cases of invasive group B streptococcal disease in the United States; and about half of these occurred in newborns (7600 neonatal cases a year) [14]. The burden of perinatal group B streptococcal disease extends beyond neonatal illness and death, and can include long-term disabilities such as hearing loss, impaired vision, and developmental problems [9, 13, 15].

Estimates of GBS colonization rates in pregnant women range from 12% to 35% [2]. Colonization rates vary by number of sites sampled and by the type of culture media used. "Selective media" (an enriched liquid medium that encourages the growth of microorganisms better than agar media and is supplemented with antibiotics to inhibit the growth of non-GBS organisms) are commercially available, and the Food and Drug Administration (FDA) recommends their use as the standard means of identifying GBS from prenatal specimens. These media can identify 80-90% of those in the carrier state. Furthermore, sampling from both the rectum and vagina as compared to just the vagina increases the recovery rate by 20% [16, 20]. Colonization can be chronic (40%), intermittent or transient [21]. Although overall colonization rates do not vary by trimester, only 4% to 7% of women who had negative vaginal and anorectal cultures late in second trimester will have positive GBS culture at delivery [21] and approximately 33% of the women who have positive GBS cultures during the second trimester (15 to 28 weeks) have negative cultures at delivery [16]. Colonization is not altered by or dependent on pregnancy, but only has consequences during pregnancy. About half of the infants born to colonized mothers are themselves colonized on the skin and mucosal surfaces as a result of passage through the birth canal or as a result of GBS ascending through ruptured membranes. The majority of colonized infants (98%) are asymptomatic. However, about 1-2% will develop early-onset disease, presenting with sepsis, pneumonia, or meningitis in the first few days of life [9].

Vertical transmission of GBS organisms from the birth canal to the fetus occurs during the labor and delivery process and as such, the length of time of rupture of the amniotic membranes is directly related to the risk of infection. Without prevention, approximately 60% to 80% of infant infections occur in the first seven days of life (EOD) [1, 22, 23]. A recent study published by Davies *et al* [1] highlights the burden of neonatal GBS disease in Canada and presents a baseline for which identified maternal and neonatal risk factors can be targeted for preventive strategies.

Rates of neonatal infection range from 0.3 to 3/1000 live births [1, 5, 20, 24]. In a Canada-wide, multi-hospital-based study, the overall rate of neonatal GBS cases was 0.44-2.1/1000 live births [1]. A case-fatality rate of 6% to 20% has been reported in recent studies [1, 2, 25, 26]. The fatality rate of GBS EOD for Canada in 1992 was 20% according to a tertiary care hospital based study [1]. A recently published study by Davies *et al* [6] reported 9% neonatal deaths among EOD cases in Alberta, during 1995-1999.

Prevention strategies for GBS EOD

The mortality, morbidity, and rapidity of onset of GBS EOD have led to numerous strategies to prevent infection in the newborn. They include active and passive immunization and antenatal, intrapartum and postnatal chemoprophylaxis.

Immunoprophylaxis

Active: Efforts to develop GBS vaccines for the active immunization of pregnant women to prevent neonatal GBS disease are underway [27-31]. A vaccine that elicits high concentrations of transplacentally transmissible immunoglobulin G (IgG) would make third-trimester immunization feasible as a strategy for preventing this devastating infection [4]. Aside from GBS disease prevention, there are many other intangible benefits of vaccines relative to IAP such as less invasive labor and peace of mind for the mother. Theoretically, a vaccine can also prevent in-utero deaths and stillbirths [4]. Although vaccination may be the ultimate solution, much more work remains before any candidate GBS vaccine reaches the marketplace.

Passive: The use of intravenous immunoglobin (IG-IV) has been proposed to prevent disease by increasing antibody titers to GBS in newborns, but this strategy cannot currently be recommended as clinical studies have not shown appreciable increase in antibody titers. This is possibly due to the variability in GBS specific antibodies in the IG-IV preparation needed to prevent GBS disease in newborn [32].

Chemoprophylaxis

Neonatal: Waiting until after delivery to give antibiotics appears to have limited impact because most early-onset infections are acquired in utero [63]. Although prevention of some cases of GBS may occur by administration of chemoprophylaxis to newborns, this is not an effective strategy as 60% infants are already symptomatic at, or shortly after birth [33]. In addition, chemoprophylaxis has been shown to be ineffective in preventing GBS-EOD, particularly in the low-birth-weight infant [34].

Antepartum: Antenatal antibiotics, administered early in pregnancy, do not prevent GBS-EOD [35-37] probably because eradicating GBS from the gastrointestinal tract is difficult, and reacquisition of the organism is common. It has been shown that even after a course of antibiotics during the antenatal period, high rates of recurrence of GBS colonization (67%) occur by the time of delivery [38]. Oral antibiotics may be useful in resolving GBS bacteriuria thus decreasing the risk of preterm labor, but they are not effective in eradicating genital colonization [39].

Intrapartum: In contrast, using intrapartum antibiotic prophylaxis (IAP), which is administered after labor onset or membrane rupture but before delivery, has been proven to be an effective way of reducing transmission of group B streptococcus from a colonized mother to her infant [17, 40]. The timing of intrapartum IAP for prevention of GBS-EOD is important. As the interval between the first dose of IAP and birth increases, the proportion of infants with colonization decreases [44]. When antibiotics are given within an hour of delivery, 43% of babies were colonized, similar to babies of untreated mothers. Only 1% of babies whose first dose was more than 4 hours before delivery was colonized. The implication of these data is that the earlier intrapartum prophylaxis is started, the better the opportunity to prevent GBS transmission to the infant.

During the 1990s, investigators focused on the question of who should receive antibiotics. Consideration has been given to treating: (a) all GBS colonized women [40], (b) all women with obstetric risk factors such as prolonged rupture of membranes, intrapartum fever, and premature delivery [45] and, (c) only those women who are GBS colonized and also have obstetric risk factors [17]. Depending on the population involved, the first two strategies above, could involve using antibiotics in a large proportion of deliveries. The first and third strategies above have been the subjects of clinical trials in which GBS colonized women were identified through prenatal cultures. The second strategy was proposed based on theoretical arguments regarding its potential effectiveness.

Although antibiotics have been proven successful in reducing the incidence of GBS in neonates [5, 46], adverse effects of widespread antibiotic use cannot be disregarded. In addition to allergic reactions and other adverse effects of the antibiotics, another hazard of IAP use is the potential selection of resistant strains of bacteria [47, 48]. Spaetgens *et al* [49] have reported resistant rates of GBS to erythromycin and clindamycin of 5.6% and 3%, respectively, whereas 20.6% of *Escherichia coli* were ampicillin resistant.

GBS studies review

Cost-effectiveness studies: No Canadian figures are presently available which assess the economic burden of GBS disease, direct or indirect. Several US studies have evaluated different GBS prevention strategies using decision analysis with cost-effectiveness as a decision criterion. Cost-effectiveness is defined here as an intervention for which the costs are considered to be justified by the benefits provided. Mohle-Boetani *et al* [18] estimated that implementation of a risk factor strategy for prevention is only cost-effective if the incidence of GBS is more than 0.6 per 1000 live births. The same study also found that universal screening (at 26-28 weeks) with selective IAP of colonized women with risk factors is cost-effective only if GBS incidence is 1.2 per 1000 live births. Rouse *et al* [19] concluded that universal IAP, risk-factor-based strategies, antenatal screening at 36 weeks and IAP to all GBS-positive mothers and all preterm

deliveries, were cost-effective strategies. Strickland *et al* [50] calculated that in geographic areas where the maternal colonization rate is less than 10%, a universal screening program is not cost-effective. Fargason *et al* [51] reported that a risk-factor-based strategy increased the cost of averting one case by 94-112% compared to 51% for a screening-based strategy. The authors pointed out that prevention strategies are cost-effective when compared with the direct costs of caring for newborns with GBS sepsis.

Table 3 compares the results of some previous economic evaluation studies. The cost per GBS EOD case was estimated in one economic analysis by Mohle Boetani *et al* (1993) to be US $33,800 (CDN $52,129)[18] and in another analysis in 1994 [19] to be US $67,229 (CDN $103,687). Total pediatric costs for the US reported by Fargason *et al* [51] in 1997 were US $41 million for a risk-factor-based strategy and US $33 million for a screening-based strategy (screening at 26-28 weeks, IAP to colonized mothers with risk factors). The differences in cost-effectiveness study conclusions may be due to variability in maternal colonization rates, the frequency of EOD and management practices of neonates born to mothers treated with antibiotics [44].

As shown in Table 3, none of the studies has compared all five potential strategies. Mohle Boetani *et al* [18] have evaluated the vaccination strategy, but have not included the screening based strategy at 35-37 weeks which is one of the strategies recommended by the Society of Obstetricians and Gynecologists of Canada (SOGC) and the Centers for Disease Control (CDC). Rouse *et al* [19] have not included the vaccination strategy (hypothetical), and neither do Garland *et al* [41], Benitz *et al* [42], or Yancey *et al* [8]. The present study has included all of these major possible strategies including the vaccination strategy. Vaccination, although currently hypothetical, may be an effective prevention strategy in the future should it be licensed.

In addition, though some of the studies are referred by authors as 'economic evaluation' studies, there are some major methodological issues with them. For example the cost-effectiveness analysis (CEA) study by Strickland *et al* [50] have not mentioned perspective and year of the study, also incremental cost effectiveness ratios are not calculated. Similarly the studies by Mohle Boetani *et al* [18] and Garland *et al* [41] as mentioned in the Table 3, have used several methods like CEA and cost benefit analysis

(CBA), but did not diferntiated between them. They also have mentioned 'societal perspective' in their study but have not included all the costs incurred such as 'indirect costs' etc.

As stated earlier, previous studies (Table 3) are primarily from the United as stated earlier, previous studies (Table 3) are primarily from the United States, and no economic evaluation studies have been published using the Canadian context. The present study has attempted to evaluate the cost-effectiveness of GBS-prevention strategies with respect to the population and costs for Alberta, which maybe more generalizable to Canada than the US studies.

Table 3: Comparisons of the results of some previous GBS-EOD studies.

Variables	Mohle-Boetani et al [18] , 1993 US $ (CDN $)	Rouse et al [19], 1994 US $ (CDN $)	Yancey et al [8], 1994 US $ (CDN $)	Garland et al [41], 1995 Australian $ (CDN $)	Benitz et al [42], 1999 US $ (CDN $)
1. Percentage of GBS-EOD cases prevented (%)					
Strategy 1	0	0	-	0	0
2	55	69	-	80	64
3	-	86	-	-	-
4	57	50	-	38	-
5	59	-	-	-	-
2. Percentage of women given IAP (%)					
Strategy 1	0	0	0	0	0
2	10	18	0	9.8	17
3	-	27	-	-	-
4	4.5	3.4	4	1.3	-
5	-	-	-	-	-
3. Total costs (million $)					
Strategy 1	294 (453)	0.19 (0.29)	-	10.7 (0.29)	-
2	228 (351)	0.69 (1.00)	-	8.62 (1.00)	-
3	-	0.085 (1.3)	-	-	-
4	278 (428)	0.112	-	-	-
5	163 (453)	(0.172)	-	-	-
4. Intervention costs (million $)					

Strategy 1	0	-	-	0	-
2	41.3 (63.7)	-	-	0.15 (0.13)	-
3	-	-	-	-	-
4	95 (146.5)	-	-	1.93 (1.64)	-
5	42 (64.8)	-	-	-	-
5. Cost per case prevented					
Strategy 1	0	0	0	0	-
2	12.9 (19.9)	-	3 (4.7)	0.27 (4.2)	-
3	-	34.8 (53.7)	11.9 (18.3)	-	-
4	28.8 (44.4)	4.2 (6.5)	22.9 (35.3)	7.4 (6.3)	-
5	10.2 (15.7)	-	-	-	-
6. GBS vaccination costs	10 (15.4)	-	-	-	-
7. Early-onset disease cost per case	33,800 (52,129)	67,229 (103,687)	22,000 (33,930)	15,590 (13,332)	13,000 (20,049)

- Not done.

Strategy 1: No intervention
Strategy 2: No screening, IAP to women with risk factors.
Strategy 3: Screening at 35-37 weeks and IAP to all colonized women
Strategy 4: Screening at 26-28 weeks and IAP to colonized women with risk factors
Strategy 5: GBS vaccination

Effectiveness of screening based strategies:

Randomized control trials (RCTs): Comparative reviews of four RCT studies are shown in Table 4. Tuppurainen *et al* [52] used the streptolatex test (sensitivity 84.2% and specificity 95.9%) to identify GBS-colonization status for women in labor. Randomization to the treatment or control group was performed using sequential sealed envelopes. 88 women were included in the treatment group and 111 women in the control group. EOD was noted in 1/88 vs. 5/111; the odds ratio (95% CI) of neonatal EOD was 0.12 (0.01-0.91) and p=0.231. Matorrus *et al* [53] randomized 121 women with positive-GBS culture during labor. Sixty women received IAP while 64 women in the control group did not receive any prophylaxis. Three cases of EOD were noted in the control group, none in the prophylaxis group; odds ratio (95% CI) was 0.0 (0-4.36). The difference was not statistically significant (p=0.137). The effect of IAP on neonatal colonization was examined by Easmon *et al* [54]. Their study included forty-nine women in the control group and thirty-eight women in the IAP group who received

penicillin or erythromycin. No newborn was colonized in the treatment group compared to 17 in the control group ($p<0.001$).

Table 4: Methodological features and outcomes of randomized clinical trials of intrapartum antibiotic prophylaxis (IAP) for neonatal GBS disease.

Studies →	**Mattoras *et al* [53] 1991**	**Easmon *et al* [54] 1983**	**Boyer *et al* [17] 1986**	**Tuppurainen *et al* [52] 1989**
Selection criteria based on GBS status	Colonized women	Colonized women	Colonized women	Heavily colonized women
Number of women in each group				
IAP	60	49	83	88
Control	64	38	77	111
Odds Ratio of neonatal EOD (95%CI)	0.0 (0-4.36)	-	0.0 (0-1.53)	0.12 (0.01-0.91)
P-values (colonization)	0.137	<.001	0.06	0.231

GBS: Group B streptococcus
EOD: Early onset disease

Boyer and Gotoff [17] conducted a RCT of selective IAP with 83 women in the treatment group and 77 women in the control group. They reported a significant decrease in neonatal colonization ($p<0.001$) but not EOD, the odds ratio (95% CI) was 0.0 (0-1.53) and $p = 0.06$, after IAP. These studies were not powered to show differences in GBS-EOD in newborns. All the studies results were consistent in showing reductions in GBS colonization in pregnant women.

Cohort studies: Allardich *et al* [55] and Yow *et al* [56] showed that IAP decreases the neonatal colonization rate significantly ($p = <0.001$). Garland and Fleignen [40] showed significant reduction in EOD ($p = 0.046$). A pooled analysis of cohort studies showed significant reduction in neonatal colonization by IAP (RR: 0.11, 95% CI of 0.05, 0.27)[44].

A meta-analysis by Allen *et al* [57] in 1993 concluded that IAP is effective in preventing GBS-EOD. The pooled odds ratio indicated a 30-fold reduction in GBS-EOD infection with IAP, odds ratio 0.03 (CI 0.0013-0.17).

Effectiveness of a risk-factor-based strategy: There have been no prospective studies to date to evaluate the effectiveness of the risk-factor-based based strategy to decrease EOD.

Physicians Prevention Practices in Canada: In a recently published study, Davies *et al* [46] surveyed family practitioners and obstetricians in two regions of Canada in 1994 Alberta and Toronto), 1995 and 1997 to document GBS prevention practices. During 1995 and 1997, more obstetric care providers were screening at least 75% of pregnant women in their practices than they were in 1994 ($p<0.001$). There was a concurrent overall significant decrease in incidence of neonatal GBS disease during the same period. This study and US surveillance [5] have supported an association between improvements in prevention practice and substantial reductions in GBS-EOD.

Canadian guidelines for GBS prevention

In a consensus statement published by the Infectious Diseases and Immunization Committee and the Fetus and Newborn Committee of the Canadian Pediatric Society and the Maternal Fetal Medicine committee of the Society of Obstetricians and Gynecologists of Canada (SOGC) in August 1994 [58, 59], the following approaches were recommended for GBS prevention in Canada.

a) Universal screening of all pregnant women at 26-28 weeks gestation with a single combined vaginal-anorectal swab and selective IAP of GBS colonized women with identified risk factors (Table 5). The rationale given for recommending this strategy was that at 26-28 weeks obstetric care providers (OCPs) would be able to identify GBS-colonized women with premature labor, and therefore, the neonates who are at highest risk of GBS infections and complications. However, the chance of missing late acquisition of GBS by the mother is great because the predictive value of cultures done at 28 weeks is limited [16]. Criticisms of this strategy included concerns regarding the predictive value of prenatal cultures. Furthermore, there is some reluctance by some

OCPs to adopt this policy since it involves introducing a new practice (vaginal-rectal swabs) that has not been routinely performed at the 26-28 week visit [46].

Table 5: Risk factors for which Intrapartum Antibiotic Prophylaxis (IAP) is recommended.

	Risk Factors
1	Pre-term Labor (<37 weeks gestation)
2	Term Labor (>37 weeks Gestation) a. Prolonged rupture of membranes. IAP should be given if labor and/or ruptured membrane is likely to continue beyond 18 hours (neonatal benefits are optimally achieved antibiotics are given at-least 4 hours prior to delivery). b. Maternal fever during labor (>38°C orally)
3	Previous delivery of a newborn with GBS disease regardless of current GBS colonization status
4	Previously documented GBS bacteriuria.

GBS: Group B streptococcus

b) No universal screening, but IAP for all women with identified risk factors (Table 5). This strategy has been suggested as being cost-effective [19] but is estimated to fail to prevent 25-30% of cases of EOD [18-20]. Reasons for this failure are infection in infants of mothers with rupture of membranes <12 hours, lack of maternal fever, and women who receive late prenatal care in whom GBS colonization is not recognized. Despite the fact that the strategy would give antibiotic prophylaxis in a large proportion of deliveries, it would at best fail to prevent at least 25% of all GBS disease cases, namely those occurring in infants born to asymptomatic carriers. Another criticism of the strategy was that it has never been studied in clinical trials.

In May 1996, the Centers for Disease Control and Prevention (CDC) in the United States, issued new GBS prevention recommendations based on data from studies suggesting that if the screening cultures were collected closer to delivery, the predictive value of the test was higher [16]. In addition, screening late in the third trimester (35-37 weeks) was associated with lower likelihood of missing women with late acquisition of

GBS [17]. These recommendations noted that the identification and management of women whose newborns might be at increased risk of GBS disease were acceptable by either of two methods [12].

c) Universal screening of all pregnant women at 35-37 weeks gestation with a single, combined vaginal-anorectal swab and the offer of IAP to all GBS-colonized women, and all mothers with preterm deliveries (Figure 2). With the screening-based approach, pregnant women with bacteriuria during the current pregnancy, who previously had an GBS-infected infant or had preterm labor, were recommended to receive IAP during labor. All women with a positive culture were recommended to receive IAP as early as possible. For women with negative culture, IAP against GBS is not recommended. The timing of screening (35-37 weeks) was justified because it addressed prophylaxis for term infants who account for over two-thirds of early-onset GBS disease. According to a study by Yancey *et al* [43], the sensitivity of late antenatal cultures for identifying colonization status at six or more weeks before delivery was only 43% and specificity was 85%. In contrast, cultures done between one and five weeks before delivery had a sensitivity of 89% and a specificity of 97%. Because of their very high risk, it was recommended that preterm infants receive prophylaxis routinely without need for culture. These guidelines suggest intrapartum antibiotics for preterm deliveries (unless a culture was already obtained and known to be negative for group B streptococcus). When this is not followed there is a chance of missing one-fourth of GBS-positive patients who might benefit from IAP [60]. Culturing specimens from both the anorectum and the vaginal introitus was also recommended as it increases the likelihood of GBS isolation by 5%-27% over vaginal culture alone [16, 61].

The screening-based strategy not only incorporates prenatal screening cultures, which identify women at the highest risk, but it also uses a risk-based approach in preterm deliveries where culture results are lacking. By moving the timing of cultures to later in gestation, there should be fewer false-negative results (or women with negative prenatal cultures who are actually colonized by the time they deliver) [67]. It also allows prophylaxis to start earlier (before complications like fever or prolonged membrane rupture develop), which may lead to higher effectiveness, or fewer antibiotic failures. It

has been shown recently that beginning antibiotics earlier during labor will be more effective in blocking transmission to the newborn [60].

Center for Disease Control and Prevention (CDC, 1996) and Society of Obstetrics and Gynecology of Canada (SOGC, 1997) recommendations.

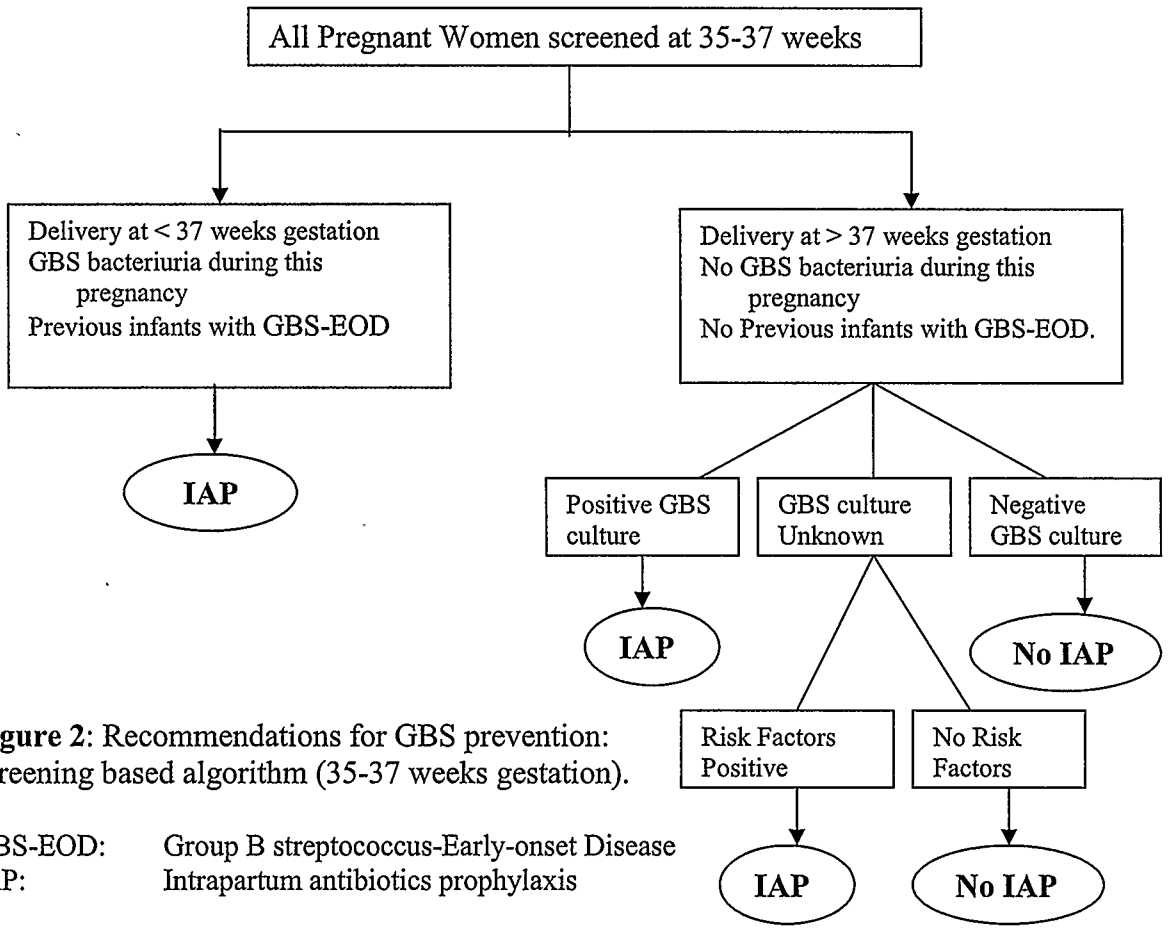


Figure 2: Recommendations for GBS prevention: screening based algorithm (35-37 weeks gestation).

GBS-EOD: Group B streptococcus-Early-onset Disease
IAP: Intrapartum antibiotics prophylaxis

d) No universal screening but IAP for all women with identified risk factors (Table 5). (This strategy is similar to the above mentioned (b) strategy recommended for Canada.). The risk-based approach (Figure 3) eliminates screening cultures for GBS.

Center for Disease Control and Prevention (CDC, 1996) and Society of Obstetrics and Gynecology of Canada (SOGC, 1997) recommendations.

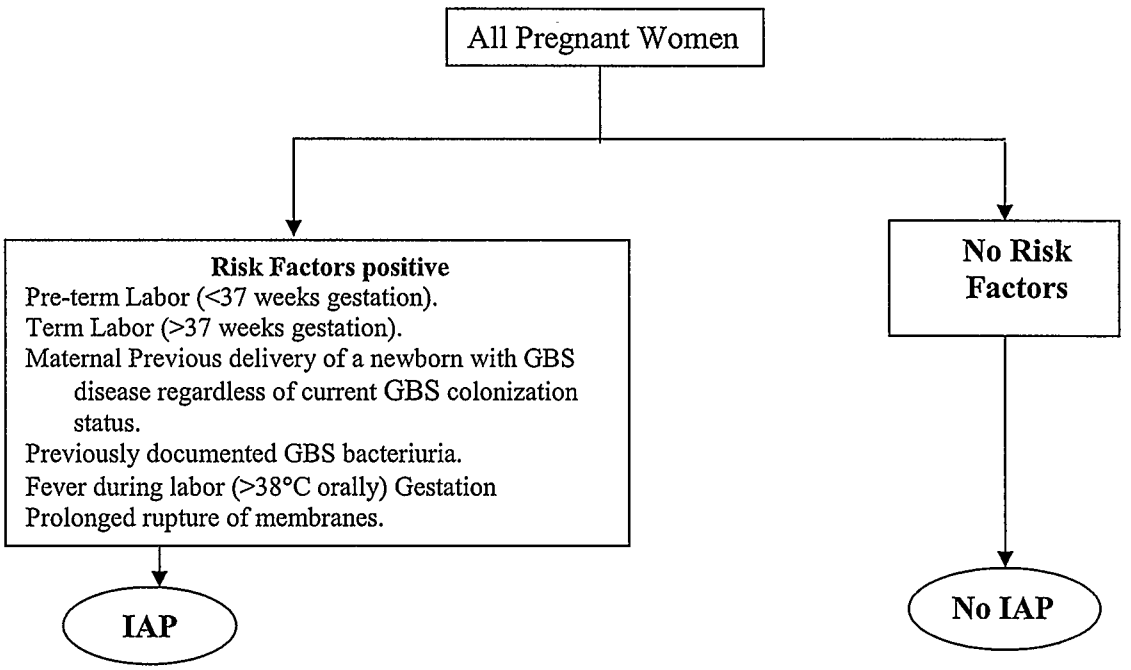


Figure 3: Recommendations for GBS prevention: risk factor based algorithm.

GBS: Group B streptococcus
IAP: Intrapartum antibiotic prophylaxis

IAP is given to women in the presence of any one of the following risk factors: preterm delivery, rupture of membranes 18 hours or longer, intrapartum fever greater than or equal to 38° C (100° F), a previous infant with GBS disease or GBS bacteriuria during the current pregnancy. This strategy should also be used in cases where universal screening is the policy, but either was not done or the test results are not available. These two strategies (c: screening-based and d: risk factor based) are not equivalent. The risk-based strategy has an approximate predicted efficacy of 60% compared with an 86% predicted efficacy of a fully implemented screening-based approach. Routine screening for GBS during pregnancy prevents more cases of EOD than the risk-based approach [62].

The risk-based prevention strategy also has several advantages. Without routine screening, using the risk-based approach is logistically easier and potentially less

expensive. It is also particularly applicable to settings in which women may receive little prenatal care and may not have been screened for GBS.

Proper choice of antibiotics is important in successful GBS-EOD prevention [60]. Adequate IAP consists of at least 1 dose of penicillin (5 million units) given intravenously at least 4 hours before birth [44]. If labor continues beyond 4 hours, penicillin (2.5 million units) should be administered every 4 hours until delivery. Intravenous administration of clindamycin (900 mg every 8 hours) or erythromycin (500 mg every 6 hours) until delivery is recommended for women allergic to penicillin [44].

In June 1997, a revised statement published by the Society of Obstetrics and Gynecology of Canada (SOGC) [63] mirrored these newer guidelines published by the CDC. The SOGC statement deems both the strategies to be appropriate "*until further Canadian data become available upon which to base the selection of the optimal strategy*" [63]. It is anticipated that the widespread increase in implementation of prevention strategies should substantially decrease the cost and suffering associated with each case of neonatal GBS disease. However, for this to occur, full adoption of all components of either guideline would be needed. This would include proper evaluation of risk factors for risk-based programs, and appropriate screening and culture techniques for screening-based programs. This ideal level of practice has not yet been reached in Canada [64].

IAP strategies may also not be consistently implemented in Canada because some populations of women may not obtain prenatal care or prenatal records are not reliably available to obstetricians at delivery (e.g., in remote parts of the country, or hard to reach populations). Additionally, in some populations, there may be a lack of adequate laboratories to allow processing of specimens, or the laboratories may not be using appropriate techniques [65]. Laboratories that fail to inoculate swabs onto selective-broth medium can miss 50% of carriers [12]. There is currently insufficient information regarding the efficacy (the extent to which medical interventions achieve health improvements under ideal circumstances) and effectiveness (the extent to which medical interventions achieve health improvements in real practice settings) of various preventive strategies to warrant universal application of a single IAP protocol in Canada.

Efforts are currently underway for the development of a GBS vaccine that may be administered to women during pregnancy and result in protection of infants through the neonatal period and beyond via antibodies passively transferred from the mother. Vaccines may be better tools than IAP against the remaining burden of invasive disease in mothers and infants because they will not only prevent GBS-EOD, but also LOD (late-onset disease) and in-utero deaths, as well as possibly minimizing adverse reactions due to antibiotics and circumventing concerns regarding resistance. Vaccines might also prevent other effects of perinatal group B streptococcal infection, such as fetal loss in mid-pregnancy and preterm delivery of low-birth-weight infants. There are also other intangible benefits of GBS vaccine such as less invasive labor and peace of mind for the mother. Such polysaccharides-protein conjugate vaccines for GBS are currently in the developmental stage [4, 27-29, 31, 34] and evaluation of their potential effectiveness is important in determining research priorities and potential cost-effectiveness or cost-benefit.

Recently published revised guidelines (2002) from the CDC [66] recommend the universal use of a screening-based strategy at 35-37 weeks gestation (a change from the previous recommendations of 1996). This change in guidelines is based on recent documentation in a large, retrospective, cohort study that indicated a strong protective effect using a strategy of screening at 35-37 weeks relative to a risk-based strategy [62]. This study used a stratified random sample from 629,912 live births in 1998-1999 in eight geographical areas in US and studied 5144 births including 312 newborns with GBS-EOD. The results showed that the risk of EOD was significantly lower among the infant of screened women than among those in the risk based group (adjusted relative risk, 0.46; 95% confidence interval, 0.36 to 0.60).

Presently, the strategy to affect the largest decrease in GBS disease in Canada remains controversial and there are currently two strategies endorsed as the standard of care. This study addresses the question, "How can the risk of GBS-EOD be minimized in Canadian newborns within the cost constraints of society?"

Limitations of current knowledge

Although the effectiveness of GBS prevention strategies has been addressed in the literature, no clinical trials have been conducted that directly compare the efficacy of the currently recommended prevention strategies. Conducting a study designed to find a statistically significant difference in efficacy between strategies might not be feasible as explained previously. Additionally, such a study may not provide directly relevant information regarding effectiveness. Although a few studies involving economic components and decision models [18, 19, 42, 64] have been described, they may not be relevant to the Canadian health care context. This study provides some cost-effectiveness data for five GBS prevention strategies in context of Alberta, including for a hypothetical vaccine, as other alternatives are viewed as appropriate until GBS vaccines achieve licensure [66].

2.2 Economic Evaluation in Health

Drummond *et al* defined economic evaluation as "the comparative analysis of alternative courses of action in terms of both their costs and consequences"[68]. Health care managers are faced with decisions to set priorities for funding different health programs within a limited funding envelope. The choices are necessary because resources are limited, while wants/needs are often not as constrained. Economic evaluation provides information regarding which alternative is preferred in terms of providing the greatest potential health benefit under constrained resources [69]. Figure 4, adapted from a review by Torrance [70], outlines the components of economic evaluation for health care program. The aim of economic evaluation is to help ensure that the benefits of the chosen health care program are greater than the opportunity costs of the program [71]. Because of the presence of scarcity, society must make choices about which health care program to fund and which to forgo. The benefits associated with foregone health care programs or opportunities constitute opportunity costs [71]. For example, in the absence of a budgetary increase, use of resources to establish a screening program for GBS colonization for all pregnant mothers would potentially result in fewer resources being available for a second program. Allocation of resources

to the GBS screening program may only be reasonable if the health gains per dollar spent exceed those of the forgone opportunity. Thus, one way to know which is the better use of resources is to estimate the costs (resources used) and benefits (health outcomes) of each program.

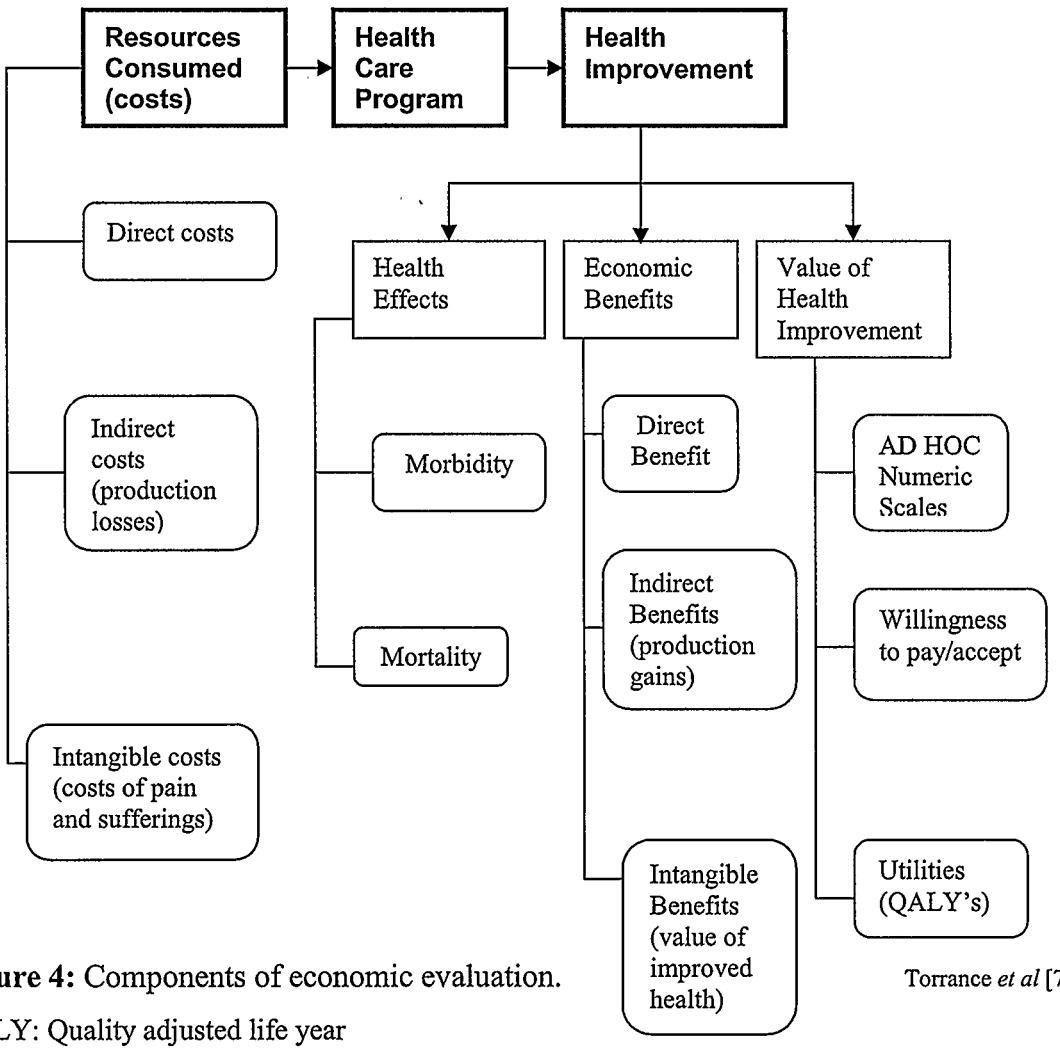


Figure 4: Components of economic evaluation. Torrance *et al* [70]

QALY: Quality adjusted life year

Different types of economic evaluations use the concept of opportunity cost, depending upon the question being addressed. If the question is one of *allocative efficiency* (e.g., GBS-EOD prevention program competes with another prevention program), then a cost-benefit study is more appropriate. Allocative efficiency is about *whether* to do something, or how *much* of it to do, rather than how to do it [69]. Cost-

benefit analysis deals with allocative efficiency, helping to decide whether a health care program should be implemented or expanded, taking into account opportunity costs incurred by not allocating the resources elsewhere. If the outcomes of two health care programs differ, then a common denominator in monetary terms is established.

If the question is one of *technical efficiency* (e.g., with the fixed amount of resource available, what is the most efficient way of preventing GBS early-onset disease in newborns?), then a cost-effectiveness analysis (CEA) or cost-utility, which addresses quality of life, is appropriate. The combination of technically efficient inputs that minimize the cost of achieving a given level of output is that which is cost effective [69]. Technical efficiency is about *how* best to deliver a program or to achieve the given objective [72].

The current study is a CEA, and thus more detail will be presented on this type of economic evaluation. CEA seeks to answer the following question: given that it has been decided that a goal is to be achieved, what is the best way of doing so or what is the best way of spending a given budget [72]? CEA is useful in comparing the different alternatives to achieve the same goals. In the present study, the evaluation compares the four GBS prevention strategies with a strategy that includes no intervention. It assesses medically relevant outcomes such as cases-prevented. Another example of a cost-effectiveness study is one by Mohle-Boetani *et al* [18] that compared the cost-effectiveness of various GBS-EOD prevention strategies for the US in 1994.

There are two forms of CEA. The first form, also known as *cost minimization analysis,* is used to determine the least costly option among several alternatives that will yield an equivalent outcome. The second form of CEA, which is used in this study, looks at alternatives with different costs and effects within a fixed budget. In this instance, the strategy that would maximize efficiency would be chosen. If an option has higher costs and lower effectiveness than another option, it is strongly dominated by that other option [73]. One alternative is said to be *dominated* by another if the first both costs more and is less effective. When this is the case, the dominated alternative normally may be removed from consideration. Whenever more than two options are evaluated in CEA, "extended dominance" can occur which is of special interest in

population-wide decisions (for example the supply of screening tests). The term extended dominance describes a state where a strategy under study is both less effective and more costly than a linear combination of two other strategies under consideration. However, decisions based on extended dominance raise questions of inequity in the provision of health care [73] because one proportion of population may receive an inferior option while the remainder will receive a superior option.

A simple framework for decision-making can further illustrate the idea of combining cost and effectiveness [74]. A new treatment that is less costly but with better outcomes than the conventional care option is preferred and is considered as a better use of health care resources. The A1 and A2 boxes of the *decision-making matrix* in Figure 5 reflect this scenario. If, without increasing the cost, a new health program can improve health outcomes, it is also an efficient use of health care resources as shown in box B1. The three boxes contain crosses where the new treatment would be dominated by conventional care. In the gray areas within the matrix, the new treatment results in lower costs but a worse outcome, or alternatively a better outcome but at higher costs. Because treating the same number of patients with this option will entail allocating more resources to them and less to others, judgment is required to decide whether extra resources should be used for the gains in health. Here it becomes a question of allocative efficiency, which is beyond the focus of CEA as described above. Alternatively, an *incremental analysis* of costs and consequences can inform us how much extra money is required to achieve a given unit of health gain from the new strategy. Incremental analysis refers to the process of estimating the additional cost per unit of outcome achieved when comparing one intervention with another (more expensive and more effective) form of intervention [69]. A ratio is produced when dividing the incremental cost by the incremental effectiveness from the two strategies. Such ratios are often referred to as "incremental cost-effectiveness ratios" (ICERs).

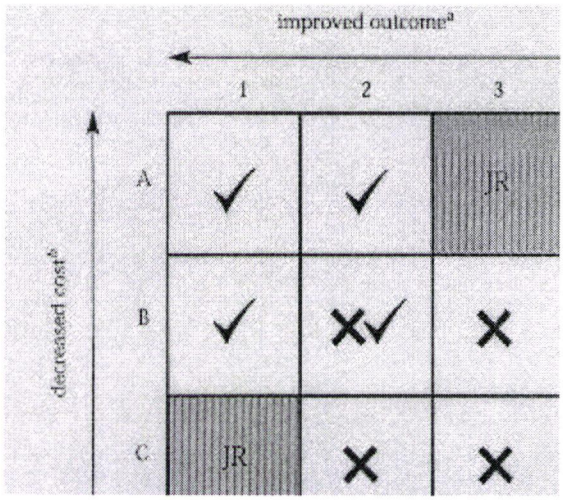


Figure 5: Decision making matrix

√= yes; X= no; X√ = indifferent; JR = judgment required.

Source: Adapted from Sackett and Oxman, eds. 1995 [91].

Thus, the ICER describes the extra cost per unit of health effect gained and aids judgments about whether such gains in health are worthwhile. The results of incremental cost-effectiveness analyses can be presented using the "cost effectiveness plane" [92] (see Figure 6). The intersection of the axes indicates the baseline position. For example, a new intervention that brought about an increase in costs overall but was also associated with improvements in effectiveness would be in Quadrant I. For a new intervention in Quadrant I, the funding decision depends on a judgment as to whether the increase in effectiveness justifies the increase in cost. Similarly, funding decisions for a new intervention in Quadrant III require consideration of the cost saving and the reduction in effectiveness. For interventions that have incremental evaluation results that move them into Quadrants II or IV, the funding decision is more straightforward.

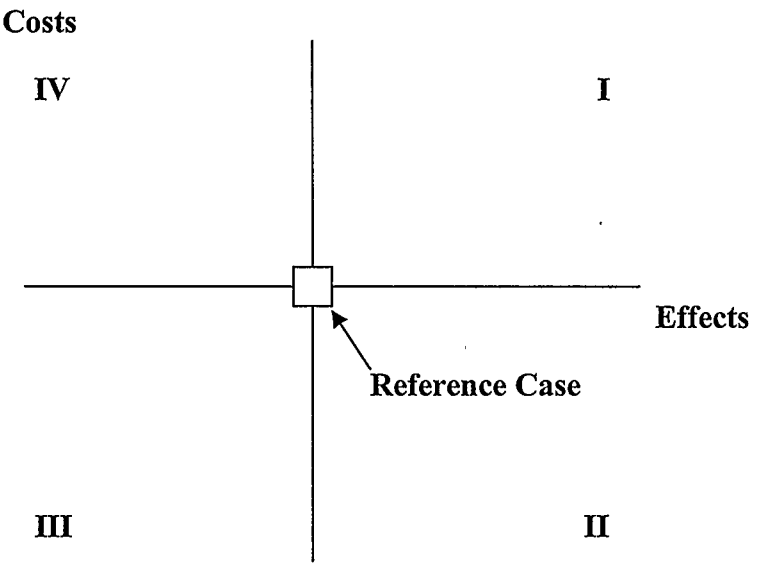


Figure 6: The cost-effectiveness plane

Adapted from Black [92]

2.3 Decision analysis

Often randomized trials among a study patient cohort are conducted in order to estimate the real costs and health benefits of alternative options or treatments. However, sole reliance on this information presents a problem. As noted by Benitz *et al* [42], there is no possibility of having a randomized clinical trial for GBS prevention strategies, as more than 100,000 women are needed for each group respectively to do such a trial. Additionally, randomized trials do not directly address effectiveness as opposed to efficacy, nor do they address the uncertainties and tradeoffs associated with a choice among alternative strategies. Decision analysis is a common method for performing an economic evaluation, using randomized trial data or good observational data as input. Decision analysis evaluates the uncertainties involved in choice of options/strategies, particularly for complex problems for which definitive, randomized controlled trials are lacking but good observational data (prospective or retrospective data) are available [75].

Decision analysis is the application of explicit, quantitative methods for analyzing decisions under conditions of uncertainty. Such analysis can be used as a

means of modeling a decision problem, using cost-effectiveness as a decision criterion [77]. Decision analysis is useful in clinical situations where uncertainty is present and where there are important tradeoffs [76]. Though decision analysis can be a useful tool in decision-making, it cannot replace the human expertise and judgment required to make good decisions [78].

Decision analysis methods

There are several approaches to decision analysis modeling. Decision analysis using decision trees is the most widely accepted method and is relevant to clear modeling of prevention effectiveness [77]. There are other forms of modeling that are commonly used in published decision analyses, including Markov models, and Monte Carlo simulation. Markov models are useful to model the transitions between different clinical conditions that may occur over time. Monte Carlo simulation can be used to simultaneously model the uncertainty associated with all variables of the model, and to "track" individual patients through time. However, because of the nature of GBS EOD prevention strategies (screening and intervention takes place during and around pregnancy and delivery time of the women, and does not involve different clinical conditions occurring over time), a simple decision tree was used here.

The decision-analytic approach suggested by Weinstein *et al* [79] has been used to set up the model used in this thesis. The basic steps of the approach, described below, are also summarized in Figure 7:

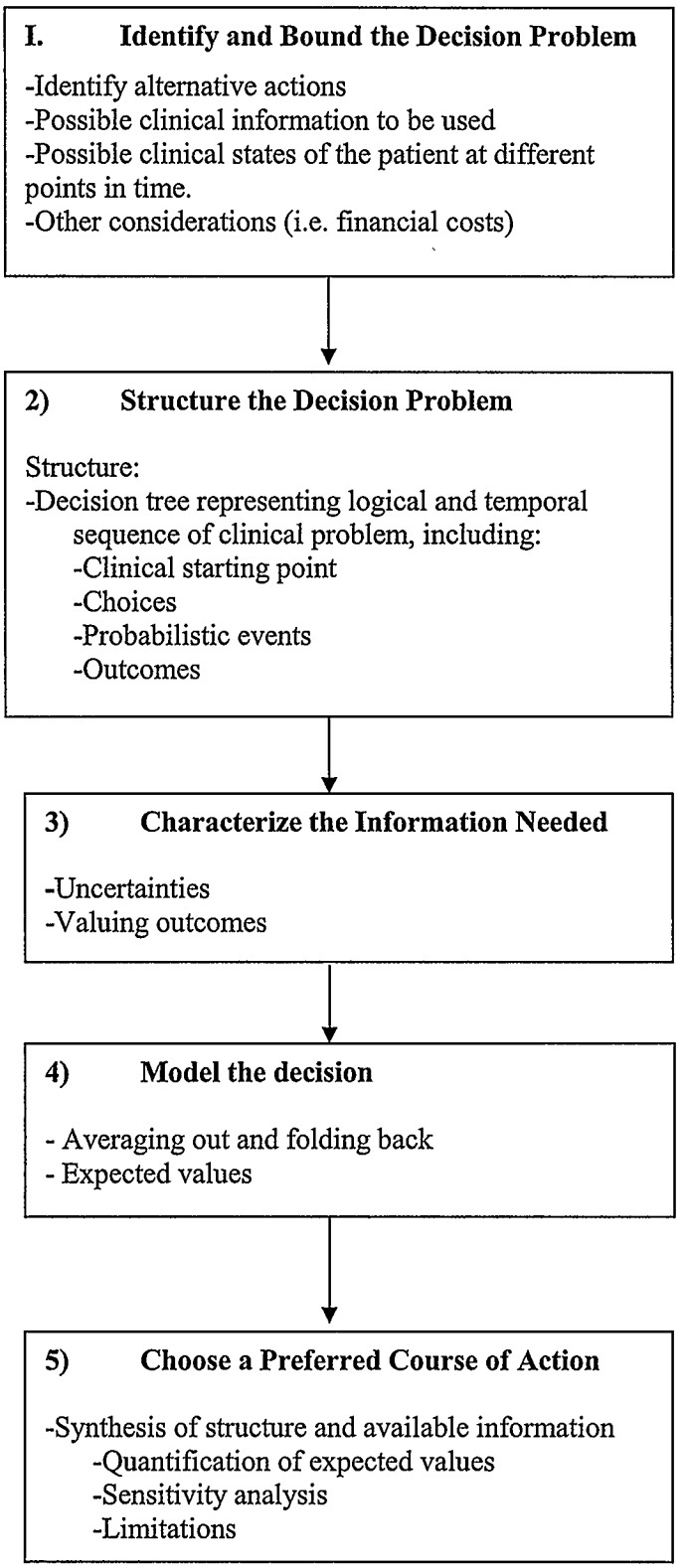
1) The first step is to identify and bound the decision problem. This involves identifying the objectives of the analysis (i.e., estimating effectiveness within resource constraints), alternative actions, and sources of clinical information. For the present study, details of this step are discussed in the Methods section. The decision-maker next specifies the possible clinical states of the patient at different points in time and other considerations such as financial costs, etc. The first step of analysis is to simply list each of these considerations. The structuring of these component parts is the task of the second step.

2) The second step in decision analysis is to structure the decision problem. After identifying the components of the decision problem, they are structured in a logical and temporal sequence. The final product of this step is a decision tree, which is especially helpful in highlighting the sequential nature of events and decisions over time. The details of decision tree structured for this study, choices, probabilistic events and outcomes, are explained later in the Methods section.

3) Step three of a decision analysis involves characterizing the information needed to fill in the structure, identifying the nature of uncertainties and valuing outcomes that are addressed in model structure. It is important to understand the sources of uncertainty, and explore sources of data that can clarify the nature of the uncertainty. Sensitivity analysis is used to explore how sensitive the results of the analysis are to the uncertainty inherent in the estimates used for variables.

4) After step three, a decision analysis involves the decision modeling. Once the decision trees are constructed and valuing of outcomes is performed, the model is analyzed by *'averaging out and folding back'*, which enables the decision-maker to compare in quantitative terms the cost-effectiveness of alternative courses of action [75]. The value of all possible branches at each chance node is *averaged out* by multiplying the probability of each branch by the value attached to it and summing the values of all branches at the node. Then *folding back* occurs along the most favorable value (e.g., the highest value if it is effectiveness or the lowest value if it is cost). Then the decision tree calculates *expected values*, or mean, which is the weighted average of the possible outcomes, the weights being the corresponding probabilities (i.e., probability-weighted outcomes). By this sequential process of averaging out and folding back along the branches of the decision node and calculating expected values, one can derive the preferred strategy for the clinical decision [79].

Figure 7: Decision analysis approach [79]



5) The final step in decision analysis is to choose a preferred course of action. For example, referring to the decision matrix in Figure 5, if a strategy is more effective in preventing GBS in newborns at the same or a lower cost (boxes A1 and B1), then this may be a preferred alternative. However, as an example if a strategy falls in box C1 in the matrix, it is considered to be more effective in preventing GBS, but it is also more expensive to use. Under a fixed health care budget, adopting this strategy will imply less resources allocated to other programs, which is the opportunity cost of funding the program. It is important to perform a sensitivity analysis on important variables to estimate the robustness of the results.

2.4 Other economic evaluation issues

Perspective of the study

The present analysis is conducted from the "health care payer's perspective" i.e., costs incurred, gained and saved are within an Alberta health care sector (Calgary Health Region, patients and care givers) including other public sectors such as long term care. Societal perspective (which incorporates all costs and all health benefits regardless of who incurs the costs and who obtains the benefits/effects) was not used in the present study. Costs are expressed in 2000 Canadian dollars. Resource costs of a health intervention or program include: capital costs (building, equipment, etc.), staffing costs (physicians, nurses, etc.), consumable costs (drugs, injections, dressings, etc.), non-patient related costs (overhead costs) and costs incurred by patients and their families (for childcare etc.) [69]. These are referred to as direct costs, which are used for baseline analysis of this study. Because the perspective of health care payer is considered in this study, indirect costs such as cost of loss of productivity are excluded from the baseline analysis (i.e., decisions that are made at a payer level do not consider these indirect costs).

Discounting

Costs and monetary outcomes must generally be *discounted* appropriately [75]. Discounting is a method used for adjusting the value of future costs and benefits. The basis for discounting is the time value of money, which states a dollar gained today is

worth more than a dollar gained in the future. Discounting has been rationalized in health economics as individuals may exhibit a "positive time preference" [80]. This means that persons tend to favor present gains in health over future gains, therefore preferring to be healthier now than in the future. There are number of reasons why individuals may have a positive rate of time preference: (a) The future is uncertain, resulting in a preference of benefits today rather than benefits in the future. (b) With positive economic growth, individuals might expect to be wealthier in future, so the incremental impact of a unit of wealth gained or lost in the future is less than if gained or lost now. (c) One can usually obtain a positive return when making a riskless investment, so there is an opportunity cost of not having resources available now [68]. Future costs are discounted to account for the time value of money, and future health benefits are discounted to account for the delay in satisfaction from these outcomes. Discounting of non-monetary benefits is more controversial, since no consensus among studies exists that states that a year of good health now is more valuable than a year of good health in the future [80]. Usual discount rates vary from 5% to 10% per year. For example, Mohle-Boetani *et al* estimated total costs of long term care for 60 years using a 5% discount rate [18]. The CCOHTA (The Canadian Coordinating Office for Health Technology Assessment) guideline [90] recommends the base case discount rate as 5% per year. They recommend using the same discount rate for both outcomes and costs to avoid paradoxical results. In the present study discounting for meningitis long-term sequelae variable was considered at a base rate of 5% per year as per CCOHTA guideline [90]. In sensitivity analyses 0% (no discounting), 3% rate for comparability with future studies required by the Washington Panel reference case [90] and 8% [79] were adopted.

Sensitivity analysis (SA)

SA involves varying the assumptions over a range of clinically plausible probabilities and costs employed in the analysis and reexamining the results to determine the effects of this variation on the conclusions of the study. In the present study, one-way sensitivity analysis was conducted to assess the effect of changes in the

baseline values (Table 6) on the cost per case prevented and on ICERs for each intervention to assess the robustness of the conclusions. This approach is useful in determining where uncertainty about a key parameter's value could have a substantial impact on the conclusion [81]. Each uncertain component of the evaluation was varied individually, while the others retained their base-case specifications. Multivariate sensitivity analysis can be useful in assessing the robustness of the estimated overall ICER to simultaneous variation in multiple variables; however, this requires simulation techniques that were not considered necessary for the present analysis.

For sensitivity analysis, the analyst must (a) choose which variables to vary and which to treat as fixed, (b) determine the amount of variation from the base value, and (c) determine how much change in the base results is acceptable or constitutes a robust finding. Thus, the results of sensitivity analysis may depend on many subjective choices made by the analyst [81].

CHAPTER THREE: METHODS

3.1 Data

Sources of data

This study was conducted with ethical approval from the University of Calgary Conjoint Health Research Ethics Board (CHREB).

For use in economic evaluation, there are various ways to collect data on cost and effectiveness, such as from clinical trials, observational studies and costing studies. However, the problem of using published data is that it is not always relevant to the analysis [68]. There are currently limited effectiveness data and no Canadian costing data available for GBS prevention strategies. As a result, only part of the data in this analysis is drawn from other Canadian sources, US studies, and the published international literature. The majority is derived from local Alberta sources (Alberta GBS study Group, Davies *et al* [6]). Population estimates of pregnant women were based upon *Vital statistics 1995-1999* [84], Alberta.

Probabilities and input variables

All the probabilities and input variables, their sources and ranges used in sensitivity analysis, are listed in Table 6. Expected value formulas were set up and DATA 3.8.5 software was used to perform the calculations.

Table 6: Summary of the variables.

Variable	probabilities	Reference/Sources	Range
Pregnant women screened for GBS in prenatal care	1	Routine prenatal care in Alberta is 100% [84]	0.80-1
GBS colonization rate in pregnant women.	0.19	[6]	0.12-0.40 [49]
Risk-factors & labor complications present	0.23	[1]	0.18-0.30
Anaphylactic reactions after IAP.	0.0001	[85]	0.00009-0.0003
Adverse reactions to GBS* protein-polysaccharide vaccine	0.003	[86]	0.001-0.004
Early-onset disease, Canada	0.0012	[6]	0.00044-0.021
Meningitis, early-onset disease	0.14	[6]	0.10-0.18
Long term sequelae from meningitis	0.21	[18]	0.18-0.25
Septicemia, early-onset disease	0.74	[6]	0.64-0.80
Pneumonia, early-onset disease	0.12	[6]	0.10-0.15
Early, infants ≥34 weeks gestation	0.98	Transplacental transfer of antibody is not consistently achieved until 34 weeks of gestation [86]	0.94-0.99
Vaccine effectiveness, infants ≥34 weeks gest.	0.90	90% out of 38,000 newborns (≥34 weeks) [18].	0.80-1
Early, infants <34 weeks gestation	0	0% out of 38,000 newborns (<34 weeks) [18].	0
Women eligible to receive IAP	1	Assumption (see text)	0.50-1
GBS-Early-onset disease after IAP	0	Antibiotics were assumed 100% effective. See text	-
Efficacy IAP	1	Assumption (see text)	0.80-1
Probability of pregnant women vaccinated	0.90	[18]	0.80-1
Discount rate for long term care (meningitis long term sequelae).	0.05	CCOHTA [90]	0-0.08

IAP: Intra-partum antibiotic prophylaxis

GBS: Group B streptococcus

Costs

Direct medical costs used in the baseline analysis of this study included the cost of interventions (IAP, vaccination, their administration and side effects costs), laboratory costs, cost of care including physician's cost for pregnant women, and costs for treating GBS disease in the newborn (including the cost of long-term care sequelae of GBS-meningitis at a discounted rate of 5%). As this study is from the health care payer's perspective, the indirect non-medical costs (i.e., productivity costs) are not included. All costs were evaluated in 2000 Canadian dollars. The estimate of daily hospital cost obtained from CHR was multiplied by a median length of hospital stay (11 days for septicemia and 17 days for meningitis) to calculate the costs for GBS-septicemia and GBS-meningitis [18]. For GBS-EOD short-term treatment and GBS-pneumonia the estimation was based on a weighted-average of all the patients in the CHR database, which consisted of patients from all three hospitals: Peter Lougheed Centre, Foothills Medical Centre, and Rockyview General Hospital. To capture the variability among patients with different disease severity and length of stay (LOS), the minimum and maximum costs of GBS disease and range of LOS were taken into consideration. The cost data was available for GBS-EOD only, showing a LOS range of 1 day-118 days. We have included the costs of adverse reactions to antibiotics and vaccination. All the cost estimates, their sources and the cost-ranges used in the sensitivity analysis are listed in Table 7.

The cost of penicillin (2 doses) and its administration (20 minutes to administer two doses) were derived from pharmacy database and an estimate of nursing wages. The cost of caring for women with adverse reactions to intrapartum antibiotics was estimated as two days of hospital costs [18] and for adverse reactions to the vaccine as one day of hospital cost in a regular ward of the hospital.

Limitations of cost estimates

The variability in the cost estimates among patients with different disease severity and length of stay may not have been captured in this study, as the data for different GBS clinical conditions such as pneumonia and meningitis were not available

from the CHR database. However, costs for GBS-EOD were available and demonstrated a large range between minimum and maximum costs (reflecting the range of LOS of 1 day – 118 days). Sensitivity analysis was performed using this range (Table 7).

Table 7: Baseline estimates of the costs.

S. No	Variable	Base case value $	Reference/Sources	Range $	Remarks
	Direct Costs				
1	**Maternal costs:** Maternal rectovaginal cultures for GBS	28.08	CLS (Calgary Laboratory services) Personal communication. (Pauline Butt on 20 April, 01)	20-30	Includes materials for specimen collection, reagents used, technical salaries, specimen transportation, report generation & distribution, and corporate and facility overhead.
2	Maternal intrapartum antibiotics including administration cost	24.00	Pharmacy, Calgary Health Region (CHR) Personal communication with Teresa Rusk on 06 July, 01)	20-30	Average 2 doses of antibiotic per patient. Spaetgens *et al* (49) have reported the IAP in use in Alberta region as follows: 58% Ampicillin, 20% Penicillin, 10% Clindamycin, 12% others like erythromycin, gentamycin etc.
3	GBS vaccination	25.00	Calgary Health Region (CHR) travel clinic.	10 - 80	Hypothetical, Average costs of most of the vaccines in Canada. Upper range is kept high to compare with other conjugate vaccine such as Prevnar.
4	Treatment for adverse reactions to intrapartum antibiotics	2151.00	Health Information Services case costs from CHR. Two days of hospital costs [18]	1075.5-3226.5	[18]
5	Adverse reactions to vaccine	1,075.50	Health Information Services case costs from CHR. One day of hospitalization cost [18].	1075.5-3226.5	[18]
6	**Neonatal Costs** Short term treatment of neonatal GBS	26222.50	[18] Av. cost GBS/day x 17 = Meningitis	-	[18]

	meningitis case				
7	Long term care for neonatal GBS meningitis with major neurological sequelae.	757,761.30	Total cost of care in a long-term care facility for dementia for 60 years.	631467-884030	Costs were based on use of nursing home care, use of medications, use of community support services by caregivers and unpaid caregiver time[87]. Varied 50 and 70 years of care for SA.
8	Short term treatment of neonatal GBS Septicemia	22,154.50	Health Information Services case costs from CHR.	-	[18]
9	Short term treatment of neonatal GBS pneumonia	23,018.50	Health Information Services case costs from CHR + Physician's costs from Alberta health and wellness, personal communication Mr. Brett Armitage, claims branch on 06 June 02.	-	Includes costs directly attributable to patients like drug cost, surgical supplies etc.
10	GBS-Early-onset disease	43,228.30	Health Information Services case costs from CHR.	1542.5-182015	Health Information Services case costs from CHR. (LOS 1-118 days)

GBS: Group B streptococcus
IAP: Intra-partum antibiotic prophylaxis
Prevnar: Pneumococcal 7-valent conjugate vaccine
Note: Health Information Services case costs from CHR from personal communication with Kelly Roy and Blair Thompson on 20 Oct, 02.

Decision tree and baseline assumptions

The decision tree for the current study shown in Figure 8 was constructed using TreeAge DATA 3.5.8 software. Time in the decision tree, by convention, flows from left to right as shown in Figure 8. The tree starts with a decision node (square) that represents the decision regarding the most appropriate neonatal GBS-EOD prevention strategy. The chance nodes (circles) here represent probabilistic events. Branches emanating from the chance nodes represent the possible outcomes of the events, leading ultimately to outcomes represented by triangular nodes/ payoffs. The structure of the tree is incomplete as shown in figure 8, as the entire tree with all the probabilistic events listed for strategies 2 through 5 is very large.

Strategy 1 starts from decision node and branches into GBS and no GBS. GBS further branches into EOD and LOD. Both of them in turn branch into morbidity and mortality (including stillbirths) branches. The morbidity branches have three uncertain clinical outcomes: 1) meningitis, 2) pneumonia, and 3) septicemia. Meningitis branches into meningitis with long-term care sequelae and meningitis without long-term care sequelae (Figure 8).

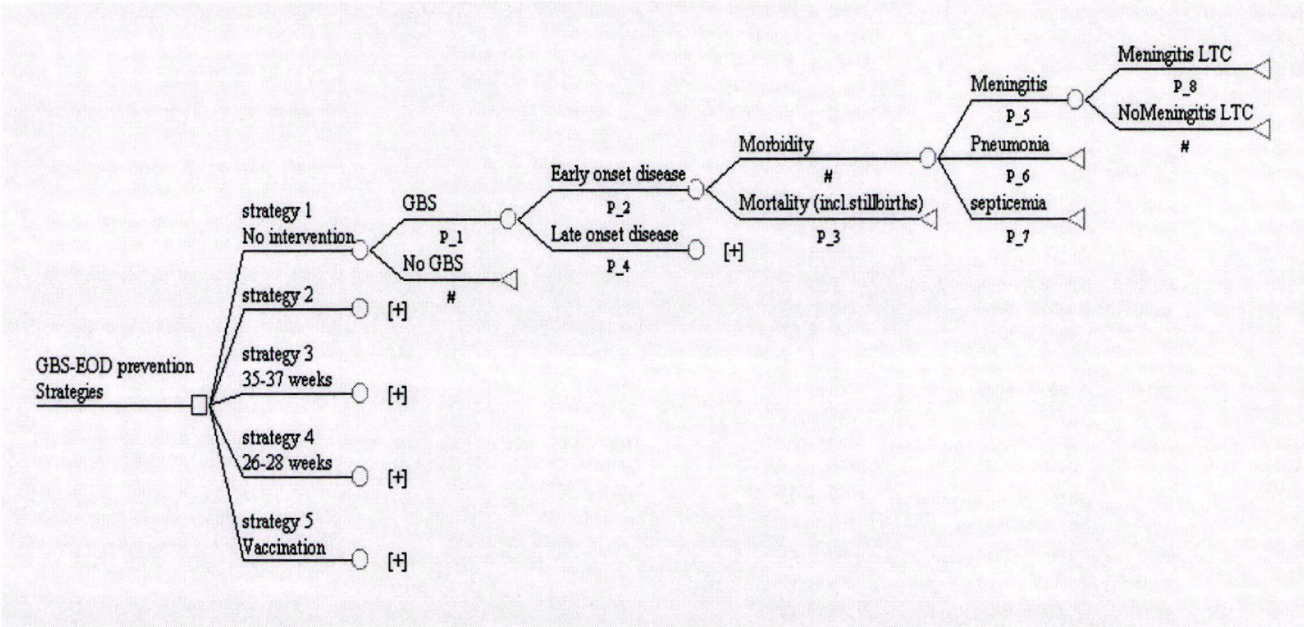


Figure 8: Decision tree: comparing four strategies for group B streptococcal (GBS) disease with no intervention. The square indicates a decision node; circles, chance nodes; and rectangles, outcomes. Baseline assumptions (probabilities) are included for each branch point.

GBS EOD: Group B streptococcus early onset disease.
LTC: long term care sequelae

Strategy 2 from decision node branches into risk factor present or absent. This further branches into IAP given or not, then into IAP adverse reaction present/absent. After that, the branches follow Strategy 1 pattern.

Strategy 3 is different from strategy 2, it starts by branching into screening at 35-37 weeks or not, then GBS colonization present or not. Then other branches continue as strategy 2.

Strategy 4 is similar to strategy 3 except the screening is performed at 26-28 weeks and IAP is offered to only colonized women who have risk-factors present, so the decision tree flows accordingly, then it is the same as strategy 3.

Strategy 5 starts from decision node dividing into two branches vaccinated or not. If vaccinated, than it divides further in gestational age >=34 weeks or less, then antibodies present or not. The end branches and payoffs are same as strategy 1.

Description of strategies (see Table 6 for baseline assumptions):

Strategy 1: No prevention strategy used. This strategy serves as baseline comparator for this decision analysis model as the "no intervention" option.

If no prevention strategies were used, the neonatal group B streptococcus disease rate would be 0.12% [1] out of which 12% of EOD cases would develop meningitis. Long term sequelae occurred in 21% of meningitis cases [18], pneumonia in 14% cases and septicemia in 74% cases [6].

Strategy 2: No universal screening but IAP for all women with identified risk factors (Table 2). This strategy may also be used in cases where universal screening is the policy but screening either was not done or the test results were not available.

The strategy developed here is based on Alberta and Canadian data. The study from Canada indicated that if screening had occurred as expected among mothers of neonates with GBS, and GBS-positive mothers had been identified as being at risk, then 46 of 78 (59%) of the EOD cases that occurred in 1992 would have been potentially prevented [1]. If 22.6% of these GBS-positive women develop labor complications [82] and if all high-risk women were identified prenatally, then IAP would be administered to 13% of all pregnant women. Based on this, we estimate that strategy 2 (risk-based strategy) would prevent 59% of EOD (as in 1992, 74% of neonatal GBS disease in Canada was EOD [1]) and 44% of all GBS cases.

Strategy 3: Universal screening of all pregnant women at 35-37 weeks gestation with a single combined vaginal-anorectal swab and the offer of IAP to all GBS-colonized women, preterm infants and infants who were not screened, but have risk factors. The SOGC and the CDC currently recommend strategy 3 as one of the two alternatives for GBS-EOD prevention.

The present study assumes that 100% of women would receive pre-natal care and that 19.5% of all women screened would be colonized with GBS [83]. These percentages are varied in the sensitivity analysis. If all colonized women received IAP, 19.5% of all pregnant women would receive IAP. Implementation of this strategy could prevent 86% of EOD among women who are screened [19]and 64% of all neonatal disease would be prevented. The percentage of prenatal care has been varied 80% and 90% in the sensitivity analysis.

Strategy 4: Universal screening at 26-28 weeks gestation with a single combined vaginal-anorectal swab and the offer of IAP to GBS-colonized women with identified risk factors only. Although strategy 4 above is not included in the most recent Canadian guidelines, it has been included in this analysis because of indications that many Canadian obstetric care providers may still be using it [46].

The present study assumes that 100% of Canadian women would receive prenatal care and that 100% of women will be screened for GBS during a routine prenatal appointment (for sensitivity analysis we have varied prenatal care for 80% and 90% women). Nineteen and half percent of pregnant women would be detected as carriers [6] and 23% of these colonized women would have risk factors present [1]. If all high-risk women received IAP then 4.5% of all pregnant women would receive prophylactic antibiotics. Forty-six of seventy-eight (59%) infants with GBS disease in this study had mothers who were GBS carriers and had labor complications [1]. Thus the implementation of strategy 4 could prevent 59% of EOD among women who are screened, and 44% of all neonatal disease would be prevented.

Strategy 5: Maternal GBS vaccination with a presumptive candidate vaccine (hypothetical). Strategy 5 is also not included in the guidelines, but a GBS vaccine that elicits high concentrations of transplacentally transmissible immunoglobulin G (IgG)

would make third-trimester immunization feasible as a strategy for preventing GBS infection in neonates.

A baseline vaccine coverage of 90% was chosen for this study considering that some patients may not accept the vaccine or not have prenatal care and also that some physicians may choose not to offer the vaccine to their patients [18]. Transplacental transfer of antibody is not consistently achieved until 34 weeks of gestation [86]. Assuming that 90% of infants born at or after 34 weeks of gestation to vaccinated mothers would acquire antibody titers transplacentally, this would prevent EOD, but no infants born before 34 weeks of gestation would be protected. Thus, 81% (90% of 90%) of GBS disease among infants born at or after 34 weeks of gestation would be prevented. Since 98% of cases of neonatal GBS disease occur in infants born at or after 34 weeks of gestation [84], vaccination of 90% of pregnant women would prevent 79% (81% of 98%) of neonatal GBS Disease. In contrast to the above four strategies, the vaccine is expected to prevent both EOD and LOD and have no impact on antibiotic resistance [18]

Other assumptions used in this study are: (a) that culture is 100% sensitive in identifying colonized women as there is no practical way to validate this assumption (b) the IAP (antibiotics) would be administered in a timely fashion according to each strategy protocol though it may not be in real practice. Failure to adhere strictly to a strategy protocol will change its effectiveness in practice [19], and (c) IAP can prevent only EOD and not LOD.

Valuing outcomes

The *total costs, average cost per case prevented, incremental costs* and *ICERs* were calculated for all the strategies. A strategy was considered inferior by dominance if another strategy yielded greater effectiveness at a lower cost. If a strategy yielded a greater effectiveness at a higher cost, then the magnitude of the extra cost needed to achieve an extra unit of effectiveness was considered. The ICER is the additional cost of one strategy as compared with another divided by its additional effectiveness.

Intervention Costs: Intervention costs for each strategy were calculated by adding all intervention costs i.e., IAP (costs of medicine and its administration), screening costs (laboratory costs), vaccination costs, maternal antibiotics anaphylactic reactions and adverse reaction to the vaccine costs.

Number of GBS-EOD cases prevented. The number of GBS-EOD cases was calculated by multiplying total number of pregnant women {total number of deliveries (38,000)} with the probability of incidence rate GBS-EOD. Then the number of GBS-EOD cases prevented was calculated by multiplying the number of GBS-EOD cases with the probability of GBS cases preventable by each prevention strategy.

Cost per case prevented: Calculated by dividing intervention costs with number of cases prevented.

Total Costs: Calculated by adding intervention costs to the treatment cost of GBS-EOD.

Cost-Reductions: Calculated by subtracting cost of treating GBS cases if no prevention strategy was used (total costs of strategy 1) with total costs of each strategy (e.g., total cost of strategy 1 – total cost of strategy 2).

Sensitivity analysis

One-way sensitivity analysis (the value of a single variable is changed and the analysis is performed again) was performed in this study to assess the robustness of the conclusions. Each uncertain component of the evaluation was varied individually, while the others retained their base-case specifications. The ranges of values used for the SA are listed in Tables 6 and 7.

CHAPTER FOUR: RESULTS

4.1 Baseline analysis

Prior to analyzing the decision tree, the validity of the decision model was evaluated to determine if the results produced by the "Strategy 1: no intervention:" option reflected the annual incidence of GBS disease in newborns in Alberta, Canada. The "Strategy 1: no Intervention:" option was structured to reflect the annual pregnancy rate in women in Alberta, Canada and the risk of giving birth to newborns with GBS disease. The analysis appears to be internally valid because the total number of cases of group B streptococcal disease produced by the "Strategy 1: no intervention:" option was 46, based on a birth cohort of 38,000 which is equivalent to the annual incidence of 1.2 per thousand live births per year noted in the previous Canada-wide study [1].

Table 8: Impact of five GBS prevention strategies in Alberta, Canada.

Results	Strategy-1	Strategy-2	Strategy-3	Strategy-4	Strategy-5
No. of mothers given IAP (%)	N/A	4940 (13)	7600 (20)	1710 (4.5)	N/A
# of GBS cases per year (%)	46 (0)	19 (41)	6 (14)	19 (41)	9 (20)
# GBS cases prevented (%)	N/A	27 (59)	40 (86)	27 (59)	37 (79)
Intervention costs (CDN.$K)	N/A	211.8	1,252.0	1,109.4	965
Cost per case prevented (CDN.$K)	N/A	7.8	31.3	41.1	26
Total Annual Costs (CDN.$K)	1,979.3	846.7	1,259.0	1,748.2	1,717
Cost-Reduction (compared to strategy 1) (CDN.$K)	N/A	1,132.6	720.3	231.1	262.3

GBS: Group B streptococcus
IAP: Intra-partum antibiotic prophylaxis
CDN.$K: Canadian dollars in thousands N/A: Not applicable

Table 8 shows the impact of five prevention strategies using baseline assumptions from Tables 3 and 4. Forty-six cases of GBS-EOD among the birth cohort of 38,000 births can be expected with strategy 1 (no intervention). Under the baseline assumptions, strategy 3 is most effective as it prevents 86% cases of GBS-EOD compared to 59%, 79%, and 59% cases by strategies 2, 5, and 4 respectively. As estimated in section 3.4, the number of mothers receiving IAP for strategy 3 (20%) is also more than strategies 2 (13%) and 4 (4.5%). Total annual costs (in thousands) for strategy 1 were $1,979.3 compared to strategies 2, 3, 4, 5 which were respectively $847, $1,259, $1,748 and $1,717 with the cost-reductions of $1,132.6, $720.3, $231.1, $262.3 respectively. Thus all the four strategies (2,3,4 and 5) reduces or save costs as compared to strategy 1 (no intervention).

Table 9 shows the CEA from the baseline decision analysis. All the costs are in 2000 Canadian dollars. The expected cost of strategy 2 is $212 thousands, the expected cost of strategy 3 is $1,242 thousands, the expected cost of strategy 4 is $1,107 thousands, and the expected cost of strategy 5 is $965 thousands (Figure 9). As shown in Figure 9 strategy 4 (screening based at 26-28 weeks) is dominated by strategy 5 (vaccination). No strategy was eliminated by extended dominance. The average cost per case prevented ratio for strategy 2 was $7,839, for strategy 3 was $31,047, and for strategy 5 was $26,090. Incremental costs of strategy 5 were $965 thousands compared to strategy 2, and $277 thousands for strategy 3 compared to strategy 5. Incremental effectiveness as 10 cases prevented for strategy 5 compared to strategy 2 and 3 cases prevented for strategy 3 compared to strategy 5. By taking a ratio of the incremental cost and the incremental effectiveness, an incremental cost effectiveness ratio (ICER) of $75 thousands as estimated between strategy 2 and 5 and an ICER of $92 thousands between strategy 5 and 3.

Table 9: Base-line cost-effectiveness analysis.

Strategies	**Cost** (CDN $ in thousands)	**Incremental Cost** (CDN $ in thousands)	**Effectiveness**	**Incremental Effectiveness**	**Cost/Eff. (Cost per case prevented)** (CDN $ in thousands)	**ICER** (CDN $ in thousands)
1	0.0	0.0	(Undefined)	-	-	-
2	212	212	27	27	8	8
5	965	754	37	10	26	75
3	1,242	277	40	3	31	92

ICER: Incremental cost effectiveness ratio
Note: The above Table excludes strategies, which are dominated in either the standard or extended sense. The "strategy 4: screening based at 26-28 weeks" is dominated by "strategy 5: Vaccination". Thus it is eliminated and not included in the table above.

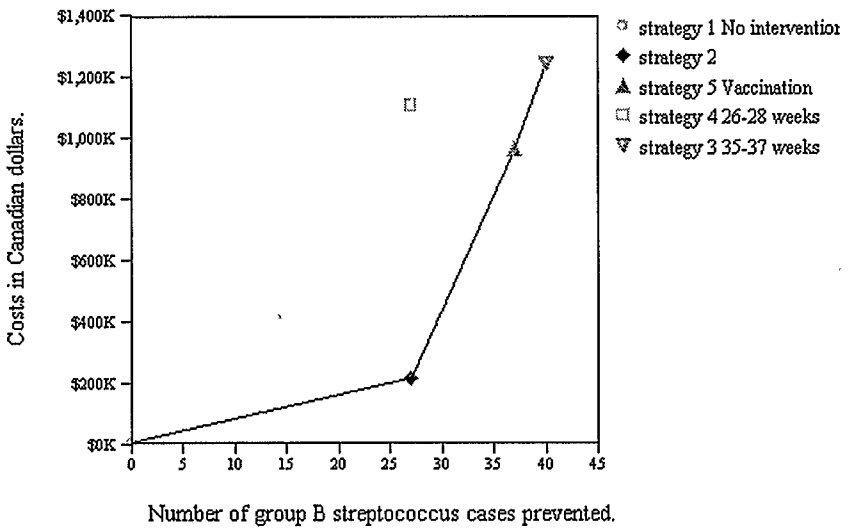


Figure 9: Cost-effectiveness graph

Data on effectiveness and costs can be interpreted in light of the "decision making matrix" explained in section 3 and shown in Figure 5. According to the baseline CEA analysis results (Table 9) strategy 3 will fall in the cell C1, greater effectiveness but costs more, thus judgment is required as to whether the more costly strategy is worthwhile in terms of additional effectiveness. Strategy 2 will fall in A3, which also requires judgment, as it is less costly, but also less effective than strategy 3. Strategy 5 falls in square B2, which is neutral, there is no difference in either costs or effectiveness.

Summary: All three strategies (2, 3 and 5) appear to be preferable to strategy 1 with regard to both costs and effectiveness (no intervention) but strategy 3, screening at 35-37 weeks, is more effective than strategies 2 and 5.

Baseline analysis cost-effectiveness analysis excluding strategy 5

Since strategy 5 (vaccination) is hypothetical, the baseline analysis cost-effectiveness analysis was repeated after excluding strategy 5 from the CEA analysis. ICER for the remaining two strategies, 2 and 5 were recalculated as shown in the Table 10 below.

Table 10: Base-line cost-effectiveness analysis excluding strategy 5.

Strategies	**Cost** (CDN $ in thousands)	**Incremental Cost** (CD $ in thousands)	**Effectiveness**	**Incremental Effectiveness**	**Cost/Eff. (Cost per case prevented)** (CDN $ in thousands)	**ICER** (CDN $ in thousands)
1	0.0	0.0	(Undefined)	-	-	-
2	212	212	27	27	8	8
3	1,242	1030	40	13	31	79

ICER: Incremental cost effectiveness ratio

By taking a ratio of the incremental cost and the incremental effectiveness, an ICER of $79 thousands is generated between strategy 3 and 2.

4.2 Sensitivity analysis results

One-way sensitivity analysis

A summary of variables, the ranges that were varied, and the results from the sensitivity analysis are listed in Table 11. Results change minimally in most of the cases where individual assumptions were varied (Table 11). The results had no impact on effectiveness even when the probability of eligible women receiving IAP was varied between 51% - 100%. The results were not sensitive to different discount rates used to perform the sensitivity analysis for the GBS long-term sequelae meningitis. Some variables, such as when GBS colonization rate in pregnant women was increased to 0.40 from 0.19, had impact on the results. Important cost variables were varied in the sensitivity analysis to capture the uncertainty relating to variability in sample data and generalizability of results. IAP costs, cost of anaphylactic reactions to IAP, and cost of adverse reactions to vaccines when varied did not reflect sensitivity to changes within these variables (Table 11). Some of the cost-variables, such as vaccination costs, and GBS-EOD case costs had impact on the results. The cost data available from CHR for GBS-early-onset disease costs have a wide range in length of stay (LOS) (1 day-118 days), which have a significant impact on the results.

Vaccination costs were increased from the baseline of $25 to $80 in SA, (see Table 11). If the per dose cost of the vaccine exceeds $30, the cost-effectiveness ratio of strategy 5 almost equals that of strategy 3 (screened at 35-37 weeks).

Table 11: Sensitivity analysis of variables

Strategies	**2**		**3**		**4**	**5**
Variables **Values**	**C-E ($K)**	**ICER ($K)**	**C-E ($K)**	**ICER ($K)**	**ICER ($K)**	**C-E ($K)**
Pregnant women screened for GBS in prenatal care						
0.80	8	8	25	60	ED	-
0.90	8	8	31	70	D	-
GBS colonization rate in pregnant women						
0.12	8	8	29	74	D	-
0.40	8	8	36	157	D	-
Vaccine coverage						
0.80	-	-	-	-	-	29
0.1	-	-	-	-	-	29
IAP effectiveness						
0.80	9	9	34	93	D	-
0.90	8	8	31	92	D	-
Adverse reactions to GBS protein-polysaccharide vaccine						
0.001	-	-	-	-	-	27
0.004	-	-	-	-	-	30
Early, infants ≥34 weeks gestation						
0.94	-	-	-	-	-	29
0.99	-	-	-	-	-	29
Vaccine effectiveness, infants ≥34 weeks gestation.						
0.80	-	-	-	-	-	29
1	-	-	-	-	-	29
Women receiving IAP (eligible to receive IAP)						
0.51	4	4	29	81	D	-
0.87	7	7	31	85	D	-
1	8	8	31	92	D	-
Vaccine coverage						
0.80	-	-	-	-	-	23
1	-	-	-	-	-	29
Vaccination costs ($)						
10						14
30	-	-	-	-	-	**32**
45	-	-	-	-	-	50
80						85
GBS-early-onset disease ($)						
1542.5	4	4	25	60	D	23
182,015	12	12	61	159	D	90

Long term care for neonatal GBS meningitis with major neurological sequelae($)							
	631,467	7	7	29	74	D	24
	884,030	8	8	31	95	D	29
Discount rates for long term care (meningitis sequelae)							
	0	8	8	31	91	D	26
	0.03	8	8	30	90	D	26
	0.08	7	7	29	89	D	26
IAP costs	20	8	8	29	85	ED	-
	30	8	8	31	92	D	-
Cost of anaphylactic reactions to IAP	1075.5	7	8	25	74	ED	-
	3226.5	8	8	31	93	D	-
Cost of adverse reactions to vaccines	1075.5	-	-	-	-	-	27
	3226.5	-	-	-	-	-	30

GBS: Group B streptococcus
D: Dominated
ED: Extended dominated
$: Canadian dollars
ICER: Incremental cost effectiveness ratio
C-E: cost per case prevented
$K: Canadian dollars in thousands
"-": Not applicable

Summary: In general, the sensitivity analysis results were robust to variation in the cost and probabilities based on the plausible clinical ranges except for few variables like vaccination costs, GBS-early-onset disease costs, and GBS colonization rate in pregnant women which had impact on the results. Varying the value of the probability variables did not have a large impact on the ranking order of cost-effectiveness of the prevention strategies. However, the cost of vaccine is quite important in terms of its cost-effectiveness compared to other strategies.

CHAPTER FIVE: DISCUSSION

5.1 Discussion

This study has provided information for health care payers involved in decisions regarding GBS disease, but there are some issues regarding the methodology and the interpretation of the results that should be considered before a conclusion is reached.

This CEA is from the health care payer's perspective and has addressed the incremental cost-effectiveness of four GBS prevention strategies compared to a 'no intervention' strategy and with one another. All the four prevention strategies (2-5) for GBS reduces or saves costs compared with no intervention at all (strategy 1), and they all have an impact on GBS-EOD. The strategies are listed in order of effectiveness in Table 9.

Strategy 4 is eliminated from consideration, as it is both more expensive and less effective than strategy 5. No strategy has extended dominance. This leaves us with strategies 2, 5 and 3 in ascending order of incremental costs and number of GBS cases prevented. Strategy 5 cannot currently be adopted, as there is no approved vaccine.

The ICER represents a measure of how efficiently the proposed intervention can produce an additional case prevention. The decision-maker prefers an intervention with a lower ICER. The ICER is the basis for deciding whether a particular procedure or set of procedures is worth its opportunity cost. One of the objectives of this analysis was to give clinicians and pregnant women affected by GBS information about effectiveness, incremental benefits, as well as the costs of choosing one strategy option over another among five prevention strategies. By taking a ratio of the incremental cost and the incremental effectiveness, an incremental cost effectiveness ratio (ICER) of $75 thousands is generated between strategy 2 and 5 and an ICER of $92 thousands between strategy 5 and 3. This study found strategy 3 to be more effective and more expensive than strategies 2 and 5. If this strategy were chosen for GBS prevention, it would incur an extra cost of CDN $92 thousands per case prevented. Since strategy 5 (vaccination is still hypothetical baseline CEA was repeated to see the how the ICER is affected after excluding strategy 5 from the analysis. The ICER actually decreased to $79 thousands

between strategy 3 and 2 (Table 10). In this case, if strategy 3 were chosen for GBS prevention, it would incur an extra cost of CDN $79 thousands per case prevented only.

Strategy 2 is based on IAP to women with risk factors based on an Alberta population-based study [6]. This strategy is useful in defining a group of women at high risk in Alberta. The risk-factor based approach (strategy 2), recommended as an alternative by the SOGC and the CDC, is the least expensive though not as effective, when compared to Strategies 3 and 5. If the values of medical costs or other variables are known for a particular region, this decision tree can be used to develop equations to estimate region-specific total costs and cost savings and these results can also be extrapolated for Canada (not done in the present study). Strategy 2 is applicable to the Alberta population; demographic risk factors for other areas need to be determined prior to estimating the effectiveness of strategy 2 or a similar situation, in other areas of Canada or other countries.

Strategy 3, prophylaxis based on screening at 35-37 weeks, is the most effective of all suggested strategies (Table 9). Using strategy 3 as predicted by our study, the SOGC and CDC recommendations, and also by Schrag *et al* [62], Rouse *et al* [19] and Benitz *et al* [42] (Table 3) would require treatment (IAP) of 20% of the pregnant population. For strategy 3 to be considered, cost-effective depends on whether the incremental cost per case prevented of $92 thousands is considered acceptable. In the light of the "decision-making matrix' explained in section 2.3 and shown in Figure 5, strategy 3 will fall in the cell C1, more effective but also costing more, thus judgment is required as to whether the more costly strategy is worthwhile in terms of additional effectiveness.

Finally, we evaluated a hypothetical vaccination *strategy* 5, polysaccharide conjugate GBS vaccines, which are currently being developed [27-29, 31, 34]. Strategy 5, vaccination of pregnant women, would prevent substantial GBS-EOD and would be cost saving compared to strategy 1: no intervention. This vaccine may also prevent perinatal mortality from GBS infection [88]. This analysis showed that vaccination, if 90% effective and if given to 90% of the pregnant population, can prevent almost 79% of GBS-EOD compared to Mohle-Boatani *et al* [18] who showed that vaccination can

prevent 59% cases (Table 13). Aside from GBS disease in newborns, vaccines might also prevent other effects of perinatal group B streptococcal infection, such as fetal loss in mid-pregnancy and preterm delivery of low-birth-weight infants. There are many potential intangible benefits of vaccines such as less invasive labor and peace of mind for the mother, which were not evaluated here.

The robustness of these CEA results was analyzed by performing one-way sensitivity analysis. Some of the variables like vaccination costs, GBS-early-onset disease costs, and GBS colonization rates in pregnant women impacted the results. When colonization rates are increased, the IAP intervention costs increases, so it increases the costs but does not affect the prevention effectiveness. In this study, the cost data for GBS early-onset disease had a wide range of length of stay (LOS), 1 day-118 days, thus having significant impact on the results. When vaccination costs are increased from the baseline of, $25 to $80 per dose (Table 11) it does not remain cost-effective. Vaccination strategy remains cost effective only if its cost per dose is kept below $30. GBS vaccine is still not available so it is hard to predict its cost, so the baseline cost is chosen as the average cost of routine vaccines like hepatitis A and B, MMR (measles, mumps, rubella) etc. Keeping in mind that it is a conjugate vaccine and likely to be costly as Prevnar is (around $90 per dose). In the sensitivity analysis, higher costs of vaccine were modeled.

In the present study, in SA, the impact of some limitations of IAPs that occur in real-life settings is assessed including simple antibiotic failure or failure from not being administered at least 4 hours before delivery [44] (probability of women receiving IAP) and poor adherence to protocol (IAP effectiveness) etc. When IAP effectiveness was varied (51% - 100%), or protocol adherence was assumed to be reduced there was minimal impact on the cost per case prevented and ICERs. In general, the results of this sensitivity analysis were robust to variation in most of the variables (cost and probabilities) based on the plausible clinical ranges.

This analysis supports the conclusions of previous analyses [18, 19, 41, 42] in that each prevention strategy evaluated does generate cost savings (Table 8). Results of this study are concordant with those of Rouse *et al* [19] and Benitz *et al* [42] that

Strategy 4 (SOGC 1994) is the least effective and a more expensive strategy, Strategy 2 (SOGC 1997) is least expensive and strategy 3 (SOGC 1997) is the most effective of the prevention strategies. Reductions in GBS-EOD cases predicted by our analysis for strategy 2, 3 and 5 are 59%, 79% and 86 %, respectively, which are similar to reported in some previous studies [18, 19, 41, 42].

Estimates of total costs are dependent on the estimated cost of screening and treatment. This analysis used cost estimates from a local source (Alberta) to minimize errors in cost comparisons. The costs of screening GBS cultures in the present study is $28.08 which is same as Mohle Boetani *et al* [18] and Yancey *et al* [8] (CDN $30.8). Also maternal IAP for this study was $24 which is comparable to previous studies [19, 42]. The estimated cost of GBS EOD case in the present study is $43,228.30, Mohle Boetani *et al* [18] was CDN $52,129 and Yancey *et al* [8] was CDN $33,930.

The decision analysis model presented here supports the notion that prevention strategies substantially reduce GBS-EOD infections in neonates. However, complete eradication of GBS-EOD is not possible and a decrease of this disease by 86% using strategy 3 (screening-based) is predicted by our study. Our analysis indicates that strategy 3 is the most effective although it costs more, so the decision-maker must decide if the greater effectiveness justifies the cost of achieving it. For GBS prevention programs, costs are incurred by Alberta Health and Wellness and the Calgary Health Region (CHR) at present, whereas benefits usually accrue to others (patients, physicians, etc.) as well as to the party who funded the program. The decision of the choice of appropriate strategy now depends on how much the patient, other stakeholders such as physicians, caregivers, etc. or the CHR are willing to spend per case of GBS prevented: $92 thousands or less. The preferred choice depends on the total budget available and on the cut-off level of incremental cost per additional unit of benefit.

Strengths of the study

This decision analysis attempted to address the shortcomings of the previous models. As shown in Table 3, none of the previous studies have compared all the five

strategies. Mohle Baetani *et al* [18] and Garland *et al* [41] evaluated screening based strategy at 26-28 weeks rather than screening-based strategy at 35-37 weeks, which is one of the recommended strategies by the SOGC (1996) and CDC (1997). As discussed in section 2.1, increased percentage of maternal vaginal colonization at term if screening is performed at 26-28 weeks results in artifactual changes in the estimated effectiveness of prevention strategies. It will overestimate the effectiveness of screening-based strategy at 26-28 weeks (versus screening-based strategy at 35-37 weeks).

Previous analyses predicted the results of predetermined prevention strategies, [8, 41, 42] but the present study as well as the study by Mohle Baetani *et al,* [18] have also evaluated the vaccination strategy. This study has predicted that the vaccination strategy can prevent 79% of GBS cases, while Mohle Baetani *et al* [18] predicted only 59 % prevention, which may be due to their use of very conservative assumptions for vaccine compliance (80%) and effectiveness (80%). Vaccination, although currently hypothetical, may be an effective prevention strategy in the future should it be licensed.

This study has counted stillbirths (GBS cases born dead) in addition to live born EOD cases. It is important to document stillbirths representing a subset of GBS-infected infants for whom IAP would not be effective, but for whom vaccines might be preventive.

Also, as stated earlier, all the previous studies (Table 3) are mostly from the US, but no economic evaluation studies have been published regarding the Canadian context. The present study has attempted to provide the cost-effectiveness of GBS prevention strategies in the Alberta context, which is more generalizable to the rest of Canada than the US studies.

Limitations of the study

Generalizability of the results or threats to external validity:

"Generalizability is concerned with the extent to which the results of a study, as they apply to a particular population and/or a specific context, hold true for another population and/or in a different context" [89]. It is important to know whether the same results will hold if the setting of the study changes. We have used certain assumptions in our analysis, some of which are derived from the results of the Alberta GBS study

group (Davies *et al*), which may not be totally generalizable to the Canadian context. Regional variations in the rates of GBS colonization or EOD may require careful consideration as individual facilities select prevention strategies.

Another type of generalizability is concerned with whether the relative cost-effectiveness observed within a study will hold true in routine clinical practice [89]. To overcome this uncertainty issue in the present study, the cost factors and discount rates were adjusted to represent probable practice levels in the sensitivity analysis to analyze the impact on the results.

Costing issues:

Indirect costs (for example the forgone earnings because of death or long-term disability) and intangible costs (e.g., costs of grief, pain, and suffering associated with infant's illness, sequelae, or death) were not included in this study. If included, they could have further captured the potential savings associated with prevention of GBS in newborns. The savings that will result from decreased maternal morbidity from GBS (e.g., bacteremia, chorioamnioitis), the prevention of GBS sepsis and meningitis that are not culture confirmed, or prevention of other causes of neonatal sepsis and meningitis, are not considered in this CEA, which would also increase the cost effectiveness of these GBS prevention strategies.

There are also cost issues regarding the variability of the severity of disease or difference in length of stay (LOS) in the CHR costs data. Because GBS disease has a broad range of severity, from asymptomatic bacteremia easily treated with antibiotics to overwhelming pneumonia or septic shock requiring extracorporial life support, reliable estimates of average direct costs for treatment of GBS case are difficult to establish. There is a possibility of appearance of 'Case or service mix bias' because the costing method used in this study has not taken into account the severity of the patient's condition or case mix group and resource consumption pattern specific to GBS disease (septicemia, meningitis etc). Failure to capture this cost variability may increase the uncertainties in the analysis. However, the present analysis has tried to capture this variability, to some extent, by obtaining the actual costs for a few conditions and

varying the range of costs in the sensitivity analysis for others (see the methods section for details).

In the present study, the costs of prematurity are included in the GBS-EOD costs (assumed to be the same for all prevention strategies), which if estimated separately from GBS-EOD may decrease the total costs further, making prevention strategies more attractive in terms of costs.

Issues regarding assumptions:

In addition, this study has assumed that, as per recommendations, all eligible women will receive IAP in the baseline analysis. In addition, women may not receive IAP for reasons such as precipitous labor, home births and human error. If this were the case then the baseline results would be very optimistic. Sensitivity analysis using these actual practices figures were performed in this study, which showed that these assumptions have no impact on the effectiveness ranking of the prevention strategies.

This study has assumed perfect compliance to the guidelines in the baseline analysis. Perfect compliance to guidelines may not always be possible for many reasons (e.g., individual patient characteristics rendering certain strategies inapplicable or caregivers using prevention strategies other than our five strategies). As per a recent study by Spaetgens *et al* [49], some physicians were found to be giving prophylaxis apart from recommended guidelines whose cost-effectiveness has not been evaluated. Also, if a woman delivers before 28 weeks, she is not eligible for strategies 3 and 4, and the same is true for a woman who receives no pre-natal care. Strategies that rely upon cultures (strategies 3 and 4) depend upon the availability of the culture results; culture failure, incomplete reporting, or recording of the results will affect these strategies. All these factors will lower the effectiveness of these prevention strategies.

CHAPTER SIX: CONCLUSION

6.1 Conclusion

GBS disease is a major cause of illness and death among Canadian newborns despite the clinical advances of the last two decades. This study has predicted the impact of current and future prevention strategies on disease and medical costs in Alberta. Results of this study and the recent evidence suggest [3] that a substantial population of GBS is preventable and that it is cost effective to attempt prevention. Universal prenatal screening at 35-37 weeks for GBS and IAP of the colonized women (Strategy 3) is likely to be more effective and cost saving in Alberta, Canada. Strategy 2 should be an option for populations in which GBS screening is impractical. It is important to monitor screening practices and the effectiveness of IAP until a vaccine or other preventable measures are available for general use. In the long term, the ideal solution will be the vaccination of women of childbearing age with a GBS-conjugate vaccine; presently under clinical trial phase [27-29, 31, 34].

This CEA for GBS prevention has important implications for future research and policy-making. It supports the SOGC and CDC recommendations that GBS prevention strategy in some form is warranted. Although alternatives to IAP, such as a vaccine, may become available in the future, implementing strategy 3 (screening at 35-37 weeks, IAP given to colonized women) remains the most effective available intervention against GBS-EOD.

6.2 Future research options

The outcomes presented in this study are cost per case prevented, which will allow comparisons of the five GBS prevention strategies: To provide a framework for valuing the health gains associated with interventions and to measure quantity and quality of life, a generic measure of effectiveness such as QALYs (quality adjusted life years) may be an alternative way to perform this analysis. (A QALY can be thought of as equivalent to a healthy year in the life of an individual).

The present study has used CEA from the 'health care payer's perspective'. Performing an alternative analysis using the broader societal perspective (including costs like production losses etc.), may make this study's results more generalizable.

The cost of GBS early onset disease may be modeled in the decision analysis again using a normal distribution with a mean and standard error drawn from the cohort group. This may help reduce the variability in the GBS costs data.

An alternative analysis using 'Canadian data' such as the average number of deliveries in Canada, maternal colonization rates, risk factors and labor complications etc might help to extrapolate the results to rest of the Canada.

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OPERATIONAL DEFINITIONS

Cost benefit analysis: A form of economic evaluation in which the outcomes as well as the costs are valued in monetary terms.

Cost consequences analysis (CCA): A form of economic evaluation in which the outcomes are reported separately from costs. A variety of measures is normally presented.

Cost-effective: The description applied to an intervention for which the costs are considered to be justified by the benefits provided.

Cost-effectiveness analysis: A form of economic evaluation in which the results are expressed as a ratio of cost per unit of health outcome. Health outcome is normally expressed in natural units (e.g., change in blood pressure or symptom free days).

Cost-effectiveness league table: A list of health care interventions in ascending order of incremental cost-effectiveness ratio (ICER). This is usually expressed in terms of cost per quality adjusted life year (QALY) gained. If the goal of the health care system is to generate as much quality of life as possible, then a list of interventions can be drawn up, from high priority (low cost per QALY) to low priority (high cost per QALY).

Cost-effectiveness threshold: The ceiling level of incremental cost-effectiveness ratio (ICER) beyond which interventions are no longer considered cost-effective. This reflects the maximum value decision-makers attach to health benefits. It is often stated in terms of cost per quality adjusted life year (QALY) gained.

Cost minimization analysis (CMA): A form of economic evaluation comparing the costs of alternative interventions that have equal effects.

Cost utility analysis: A form of cost-effectiveness analysis in which the results are expressed in terms of cost per quality adjusted life year (QALY) gained.

Direct costs: The value of those resources directly involved in providing health care, such as the time of health care professionals, cost of medicines, equipment and patient costs such as travel to receive treatment.

Discounting: The process by which the streams of future costs and/or benefits (beyond 12 months) are converted to equivalent present values.

Discount rate: The rate used in a discounting formula to convert future costs and/or benefits into equivalent present values.

Dominance: The property characterizing an intervention that has lower costs and the same or greater benefits, or the same costs and greater benefits, than an alternative.

Economic evaluation: A comparative analysis of two or more alternatives in terms of their cost and benefits.

Effectiveness: The effect of a treatment as measured in the usual clinical environment.

Efficacy: The effect of a treatment as measured in the controlled environment of a clinical trial.

Efficiency: The allocation of resources in such a way as to maximize the total amount of benefit.

Health economics: The application of the theories, tools and concepts of economics to the topics of health and health care. Health economics is concerned with the allocation of scarce resources to improve health. This includes both resource allocation within the economy to the health care system and within the health care system to different activities and individuals.

Incremental cost-effectiveness ratio (ICER): The difference in costs between one intervention and an alternative, divided by the difference in outcomes.

$$\text{ICER} = \frac{(\text{cost treatment A}) - (\text{cost treatment B})}{(\text{outcome treatment A}) - (\text{outcome treatment B})}$$

Indirect costs: The impact of illness and treatment on the ability to work, paid and non-paid work time and leisure time. Also known as productivity costs.

Intangible costs: The pain and suffering that result from undergoing a treatment. This is rarely included as a cost in economic evaluation, but may be captured in part by quality of life measures.

Opportunity cost: The benefit that a resource would yield in its best alternative use. This is the benefit forgone as a result of using the resource. Although for practical purposes the cost of a resource is generally expressed in monetary terms, in some cases there will be no financial payment – for example in the case of a voluntary caregiver.

Quality adjusted life year (QALY): A measure of the benefit of health care that combines the impact on expected length and quality of life.

Randomized trial: A study in which patients have an equal chance of receiving one of several treatments, often including a placebo.

Resources: Inputs into the production of health care, products, and services from the economy in general. These include health care professionals' time, hospitals, drugs, equipment and patients' time undergoing treatment (see direct costs). A person's availability for, and capacity to, work may also be a relevant resource (see indirect costs).

Scarcity: The fact that there are insufficient resources to undertake every beneficial activity. This can influence the choices made between alternative courses of action (see prioritization/rationing).

Utility: In economic evaluation, this term is often used to indicate the value individuals attach to different outcomes. It is often used in quality adjusted life years (QALYs) to weight periods of time in different health states.